Effect Of Antibiotic Use On Respiratory Illness

And

On Antibiotic Resistance In Children

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Amendments

Page	Sentence	Incorrect	Correct
15	24	Bacteria	Bacterium
16	2	*Mycoplasma Pneumoniae*	*Mycoplasma pneumoniae*
16	5	*And anaerobes*	And anaerobes
21	19	A pathogenic	Pathogenic
22	14	Acetaminophen	Paracetamol
23	9	*Group A streptococci*	Group A streptococci
23	11	Streptococci was	Streptococci were
25	23	URI	URTI
27	3	Bacteriocidal	Bactericidal
28	11	59% of Staphylococci	59% of staphylococci
29	6	PBPs	Penicillin binding proteins
29	27	Fluroquinolones	Fluoroquinolones
32	3	Micoorganisms	Microorganisms
45	9	Untill	Until
45	18	Receptionists(Appendix 3)	Receptionists (Appendix 3)
47	9	Monitor the pneumococcal	Monitor pneumococcal
85	14	One antibiotic	Cotrimoxazole

This is to confirm that, unless otherwise stated, this thesis is entirely my own original work, conducted through the National Centre for Epidemiology and Population Health of The Australian National University.

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Abstract

Background

The pneumococcus (*S. pneumoniae*) is a common cause of many serious and life threatening infections, including pneumonia, bacteraemia and meningitis, and is also a common bacterial cause of acute respiratory infections (ARIs). For the last decade, pneumococci have become increasingly resistant to penicillin and many other antibiotics. This trend of increasing antibiotic resistance, especially resistance to penicillin, is of particular concern in young children. Children frequently suffer from ARIs and penicillin is the drug of choice for pneumococcal infections. However, the emergence of penicillin resistance has made the choice of therapy for pneumococcal infections more difficult. Pneumococci, once acquired, persist for prolonged periods of time in children and are highly transmissible among children in settings like day-care centres. Recently, rapid increases in the incidence of infection with penicillin resistant pneumococci (PRP) have been reported worldwide. In this thesis I have explored the likelihood that reduced use of antibiotics in children could curtail the upsurge of penicillin resistance in pneumococci without increasing morbidity from respiratory illnesses in children.

Research questions

1. Is the rate of carriage of antibiotic resistant pneumococci higher in children who consume more antibiotics?

2. Does the use of antibiotics in ARIs alter the severity of acute respiratory illness?

Methods

I conducted a prospective cohort study of 502 children, who were under two years of age at recruitment. This study was part of a randomised controlled trial of clinical practice guidelines as an intervention to reduce antibiotic prescribing for acute respiratory infections in children. The trial was conducted between September 1997 and November 1999 in the Australian Capital Territory (ACT). Respiratory illnesses and treatments were recorded by parents in a daily diary. A nasal swab was collected from the children four times during the study period to monitor pneumococcal resistance to antibiotics.

Pneumococci isolated from the children were tested for their sensitivity to antibiotics. Multivariate analysis was performed to explore the relationship between antibiotic use

and antibiotic resistance. The effect of antibiotic use on respiratory illness was also examined.

Results

Isolation of PRP was significantly associated with the use of a beta lactam antibiotic during the previous two months (adjusted OR 2.03, 95% CI 1.15-3.56, p=0.01). The association was also observed by multivariate analysis for children who received either only penicillins or only cephalosporin during the previous two months. However, the odds of carrying PRP was about five times higher in children who had received both antibiotics during the two months compared to the children who did not receive any beta lactam antibiotic during the period (adjusted OR 4.67, 95% CI 1.27-17.09, p=0.02). A dose-response effect was observed; the rate of penicillin resistance increased with increases in the duration of total beta lactam use during the six months before swab collection.

I performed multiple linear regression analysis to detect the effect of antibiotic use on the severity of an episode of respiratory illness. Antibiotic use in an episode did not change the severity of a less severe respiratory episode (beta coefficient 0.008, Robust standard error 0.027). Antibiotic use failed to show a beneficial effect even in more severe episodes: beta coefficient was 0.07 for episodes that received antibiotics on the first visit and was –0.005 for episodes that received antibiotics on the second visit.

Conclusion

Reducing antibiotic use in ARIs is likely to reduce penicillin resistance in the community, without compromising clinical care of children. These findings suggest that implementation of guidelines to reduce antibiotic prescribing for ARIs in Australian general practice would curtail the increase of pneumococcal resistance to penicillin.

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Chapter 1 Introduction

1.1. Overview

Acute respiratory infections (ARIs) are common causes of childhood morbidity and mortality around the world. Despite a fall in mortality from ARIs in Australia, ARIs remain the most frequent reasons for paediatric encounters in GPs' surgeries in Australia.[1] The common ARIs in children include upper respiratory tract infections (URTIs), acute otitis media, tonsillitis and acute bronchitis. Regardless of etiology, antibiotics are widely prescribed for ARIs worldwide, although over 90% of respiratory infections are of viral origin.[2] In Australia, respiratory infections constitute the reason for 55% of all antibiotic prescriptions.[1] Essentially this current pattern of antibiotic prescribing not only costs the community, but is also believed to contribute to the problem of antibiotic-resistance among community-acquired respiratory pathogens such as *Streptococcus pneumoniae* (*S. pneumoniae*/pneumococci). Pneumococcal resistance to penicillin is of concern because penicillin has been the drug of choice for pneumococcal infections. The prevalence of penicillin-resistant pneumococci is growing rapidly in Australia. The rate was 1.7% in 1989 and increased to 6.7% in 1995[3] and 25% in 1997.[4] The cause of this alarming increase in antibiotic-resistance is not clearly identified, although cross-sectional studies have demonstrated an association between prior antibiotic use and antibiotic-resistance.[5,6]

It is possible that more judicious antibiotic use might help to combat the rapid increase in antibiotic-resistance. In doing that, a vital question is whether reduced antibiotic use would result in poorer clinical outcome. The central research question in this thesis is whether less use of antibiotics in treating children's acute respiratory infections reduces the level of penicillin-resistance without compromising clinical care.

To answer this question we elected to study children and their GPs. Most of the antibiotics used in humans are prescribed from general practice.[7] Children under two years of age were recruited as study subjects and followed for two years because under the age of five years children are a recognised susceptible group for respiratory infection, high consumers of antibiotics and important sources of spread of antibiotic-resistant bacteria.[5]

The current situation of antibiotic-resistance is explored in Chapter 2. I explore the evidence from the literature suggesting the association of antibiotic use with antibiotic-resistance. The effectiveness of antibiotics in acute respiratory infections is also reviewed in this chapter.

In Chapter 3, I outline the methodology used in this study. This study was conducted as a prospective cohort of 502 children for 25 months within the framework of a randomised controlled trial (RCT). The chapter describes the process of recruitment of study participants, methods and instruments of data collection and methods of statistical analysis.

The results of recruitment of the cohort and characteristics of the study participants are described in Chapter 4. In Chapter 5, I present the results of four sets of nasal swabs, that were collected from the children during the study. The results demonstrate the changes in pneumococcal carriage and antibiotic-resistance in children over the two years of the study period. Chapter 6 presents the association of previous antibiotic use with carriage of penicillin-resistant pneumococci in the children. The multivariate analysis included pneumococci isolated from the four sets of nasal swabs and antibiotic use during the study period. Chapter 7 details the respiratory episodes experienced by the children of the late-intervention group during the first 18 months of the study. It also documents the association between antibiotic use in an episode and the severity of the episode.

1.2. Researcher's role

Professor R. M. Douglas, National Centre for Epidemiology and Population Health (NCEPH), ANU received a grant from the General Practice Evaluation Program (GPEP) to evaluate clinical practice guidelines in acute respiratory infections. Ms Eileen Wilson (another PhD student) and I planned the detail and implemented the project. Although both of us worked closely in the day to day management of the project, we had distinct domains of the research within it. Ms Wilson concentrated on the RCT aspect of the project. I concentrated on the issue of antibiotic-resistance and illness outcomes in the study cohort.

Together with Professor Douglas, our joint supervisor, we recruited study participants, managed the RCT and its extensive database including the development of guidelines, preparing the instruments and collection of respiratory diaries. The development of

research questions, design, and implementation of the work on antibiotic-resistance and illness analysis were entirely my own work. The methodology for swab collection and laboratory procedure was prepared under the guidance of Dr Peter Collignon, Canberra Hospital. Ms Helena Beltrami and Ms Letitia Toms performed the laboratory procedures in the Microbiology Department of the Canberra Hospital. Dr Louis Pilotto was closely involved in the project especially during recruitment of the study participants. The methods for statistical analysis were developed under the supervision of Dr Leslee Roberts, Professor Louis Pilotto and Ms Robyn Attewell.

Chapter 2 Review of literature

2.1. Overview

The spread of antibiotic-resistance is one of the most important emerging infectious disease threats in the world. In recent years concerns have been raised because of the rapid increase in resistance in community-acquired pathogens such as pneumococci. Antibiotic use in young children may have contributed to this increase in antibiotic-resistance. Young children frequently suffer from acute respiratory infections (ARIs) which constitute a major reason for antibiotic use. Although most ARIs in children are of viral origin, pneumococcus is the major bacterial pathogen when bacteria are implicated with ARIs. Therefore, children may be an important focus of antibiotic-resistant pneumococci. Organisms persist for prolonged periods of time in children and are highly transmissible in child settings like day-care and school. Resistant pneumococci may be acquired by children from day-care centres and may subsequently spread to the families and then to the community.[8] The evidence of the role of antibiotic use in ARIs in children and in development of antibiotic-resistance is reviewed in this chapter.

2.2. Acute respiratory infection in children

ARI is a syndrome complex consisting of clinical conditions of varying etiology and severity. Traditionally, the syndromes of ARI are classified on the basis of anatomical location into upper (URTIs) and lower respiratory tract infections (LRTIs).[9] Common URTIs in children are: common cold (non-specific URTI), sore throat, otitis media and sinusitis. Common LRTIs are: bronchitis, bronchiolitis and pneumonia.

2.2.1. Incidence

ARI is the most important cause of childhood morbidity and mortality around the world. Most of the general practice consultations for ARI are for URTIs, which account for 7.1 per 100 encounters in contrast to 3.5 per 100 encounters for LRTIs. Overall, ARI causes four and a half million childhood deaths each year, accounting for 30% of all deaths in childhood.[10] The majority of these deaths occur in the developing countries from pneumonia.[11] Mortality from these infections has fallen in developed countries owing to

the advent of potent antimicrobial drugs and vaccines against respiratory pathogens. However, ARI remains the leading cause of morbidity in developed countries.[12]

Children under five years of age are the major sufferers from ARI. Globally, children of this age group experience six to eight episodes of ARI per year.[13] The average Australian child experiences five to eight respiratory infections annually which is similar to other countries.[14] Respiratory problems account for 40% of all reasons for which children are taken to GPs.[1] Irrespective of age in Australia, ARIs account for 20% of all medical consultations, 30% of absences from work and 55% of all antibiotics prescriptions.[1]

2.2.2. Etiology of ARIs

It has long been apparent that the known bacterial pathogens account for less than 10 per cent of acute respiratory infection. Most acute upper respiratory infections are caused by viruses including those that cause predominantly nasal symptoms and those that cause pharyngeal exudate, fever, and adenopathy. Bacterial secondary infection does not occur and this explains the absence of beneficial effects from antibiotics (Coriell, L. L).[15]

Although the majority of the ARIs are of viral origin, bacterial agents can also cause them. ARIs of viral origin are usually mild and self-limiting.[16] In contrast, bacterial infections are relatively severe.

Viral agents mainly involve the upper respiratory tract.[2] The overwhelming majority of common colds, pharyngitis and tonsillitis are caused by viruses and the commonly implicated viruses are rhinovirus, coronavirus, Epstein-Barr virus, coxsackievirus and herpes simplex virus.[17] However, a few cases of pharyngitis can be primarily caused by bacteria, *Streptococcus pyogenes*. Otitis media and sinusitis are generally considered bacterial infections. For example, a pathogenic bacteria is isolated from 50-70% of middle ear fluid in children with otitis media and virus alone is isolated from 20-30%.[18] However, both bacteria and virus can be isolated from another 20-30% of children with otitis media.[19] The common bacteria frequently associated with these infections are *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.[20,21]

Respiratory syncytial virus (RSV) is the most common cause of LRTIs in infants and young children.[22] About 1400 nonbacterial agents were isolated from children with lower respiratory disease seen in a paediatric group practice from 1963 to 1971. Among

these 1400 agents, 75% were RSV, parainfluenza virus Types 1 and 3 and *Mycoplasma Pneumoniae*.[22] Bacterial co-infection can occur with viral infection and the rate of co-infection varies in different studies ranging from 1.2%[23] to 48%.[24,25] The recognised bacterial pathogens for LRTIs are *S. pneumoniae, H. influenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma spp. and anaerobes*. Among the LRTIs, pneumonia is considered a more serious infection, especially in developing countries, where bacterial agents can be isolated from as high as 62% of cases and viral agents can be isolated from 17-40%.[12]

2.2.3. Risk factors for ARI

Age and sex

The incidence of ARI is inversely related to age, peaking at four to nine infections per year in the first two years of life, dropping to three to four by school age and remaining at two to three per year for adults.[22,26] However, the frequency of pneumonia is highest among both the very young and the very old.[27]

Several studies have reported a slightly increased incidence of ARI in young male children.[26,27] However, in older children a reverse pattern has also been documented. A more recent study of viral chest infections found no differences in incidence by sex.[28]

Socioeconomic status (SES)

The risk of ARI associated with lower SES is not always consistent. In one study, families with incomes below the poverty line were associated with increased mortality from ARIs in children;[29] this finding was also supported by Monto and co-workers.[26] However, Gardner et al. used a combined measure of family income, insurance status and parental education level to measure SES and found lower SES to be related to LRTIs but not to URTIs.[30]

Crowding

Crowding has been a well-documented risk factor for respiratory infections. General conditions of crowding may favour the transmission of illness. Woods in 1927 reported a highly significant correlation between overcrowded housing and pneumonia mortality in England and Wales, and the strongest correlations were found in the 0-5 years age group.[31] This finding was supported by Payling-Wright et al.. in 1945.[29] The number and age of siblings in families predicts the incidence of ARIs in children.[30,32]

In developed countries, the increasing use of day-care centres for children has become another leading source of transmission of ARIs because of crowding. Children attending group day-care centres are at increased risk of ARIs than other children.[30,33] Approximately one-third of all URTIs among day-care attenders and two-thirds of all ear infections among full-time day-care attenders were attributable to day-care attendance.[34,35]

Nutrition

Malnutrition is widely believed to be associated with an increased risk of LRTIs, especially pneumonia. In a two-year ambulatory study of lower respiratory illnesses, Berman et al. found that the greatest morbidity and mortality occurred in those children who suffered moderate or severe malnutrition.[27] Since malnutrition is closely related to crowding, poverty, poor education and poor housing in developing countries, it was difficult to identify an independent effect of this factor on risk of respiratory infection.[27]

2.2.4. Treatment of ARI

Globally a substantial amount of antibiotic use in children is for ARIs. Antibiotics are widely used for respiratory infection in children regardless of whether it is bacterial or viral.[36] In the United States, respiratory infections account for more than three-quarters of the antibiotics prescriptions annually.[37] The situation is even more serious in countries where antibiotics are available without a prescription. Self-medication with antibiotics before being seen by a health provider is well-documented in both developed and developing countries.[38-40]

Treatment of ARIs remains the subject of controversy between scientists and medical practitioners. As 90% or more of the respiratory infections are viral,[2,16] antibiotics should not be the treatment of choice. Several studies in both developed and developing countries concluded that antibiotic treatment in most of the ARIs neither shortens the course of illness, nor prevents the development of complications.[13,36,41]

In general, Australia has a very high rate of antibiotics use compared with other developed countries.[42] Antibiotics are prescribed for 51% of consultations for upper respiratory tract infections, 79% for acute bronchitis, 93% for tonsillitis and 77% for acute otitis media.[1] There have been strong suggestions over recent years that the

prescribing of antibiotics in Australia is unsatisfactory because of overuse of the broad-spectrum drugs at the expense of simpler, cheaper and safer drugs.[43]

2.2.5. Effectiveness of antibiotic use in ARIs

A major portion of antibiotic use in humans is from general practice. Common ARIs frequently seen by general practitioners (GPs) are common colds, sinusitis, pharyngitis, otitis media and bronchitis, and approximately three-fourths of all outpatient antibiotics have been prescribed in recent years for these five conditions.[37] While pneumonia and bronchiolitis are more severe acute conditions, sufferers are not usually treated as outpatients. To review the effectiveness of antibiotics on ARIs, five common ARIs that are usually treated from general practice are individually evaluated in this section.

Nonspecific upper respiratory tract infection (common cold)

The International Classification of Health Problems in Primary Care (ICHPPC-2) defines the common cold as an illness with evidence of acute inflammation of nasal or pharyngeal mucosa and the absence of other specifically defined respiratory conditions, e.g. streptococcal tonsillitis, laryngitis, bronchitis, pneumonia, asthma and hay fever. The common cold is an acute illness associated with one or more of the following symptoms: runny nose, sore throat, fever, cough with or without productive sputum.

Children younger than five years of age experience three to eight episodes of cold per year[44,45] and most of them are caused by viruses. However, in 1969, 95% of the physicians surveyed in USA gave one or more prescription drugs for the common cold, about 60% of which were antibiotics.[46] This practice is common in other countries as well. In a New Zealand study, Mc Gregor et al. found that 78% of the patients in general practice received antibiotics for common cold and about one third of them received broad-spectrum antibiotics.[47]

The efficacy of antibiotics in the treatment of common cold has been the subject of many review papers. One review conducted by Arroll and Kenealy in 1999 for the Cochrane Library[48] assessed the effect of antibiotics in resolution of symptoms and rate of recovery from common cold. Seven randomised controlled trials involving 2,056 people aged between 6 months and 49 years were included in that analysis. The group treated with antibiotics did not have a reduction of symptoms or duration of illness compared with the group that received a placebo. Moreover, the antibiotic-treated

group had a significant increase in side effects of antibiotics, including diarrhoea and vomiting.

Another meta-analysis by Gadomski in 1993[13] specifically looked at the effect of antibiotics to prevent LRTIs after a common cold. This study, which included five RCTs, suggested that there was no beneficial effect of antibiotic treatment of the common cold in preventing progression to LRTIs. This review also suggested no significant difference in clinical resolution of symptoms between antibiotic and placebo groups. One of the trials, however, reported more side effects, such as, diarrhoea, in the antibiotic group.

Ackerman[49] conducted a prospective double-blind study of 60 infants to assess the effectiveness of treatment in common cold. Three groups of infants were compared for duration and severity of illness and also for complications after providing 10 days of penicillin V or tetracycline or glyceryl guaiacolate. The percentage of clinical improvement after 48 hours of treatment was equal in the three groups. The mean duration of fever was 2-3 days in all groups. There was no difference in the rate of complications between the three groups.

Hardy and Traisman[50] conducted another double-blind study of 217 children under 14 years of age in an outpatient clinic. The children had a temperature above 38.3 C for 12 hours or more and physical examination revealed no positive findings, except nasopharyngitis. They were treated either with a placebo or penicillin or chlortetracycline or sulfisoxazole every six hours for four days. The use of antibiotics did not decrease the duration of symptoms or the incidence of complications.

Another prospective double-blind study compared the effectiveness of antibiotics versus placebo on 781 children with a common cold.[51] In children who did not develop any secondary bacterial infection, fever lasted for a mean of 3.6 days regardless of treatment. Fever lasted 3.7 days in the placebo group and 3.5 days in the antibiotic group among the children who developed complications. The rate of complication was not different between groups.

There is thus substantial evidence that antibiotic use is not beneficial in the treatment of common cold.

Sinusitis

Sinusitis is a frequent diagnosis and also a common reason for antibiotic prescription in children.[37] Sinusitis is defined as an inflammation of the sinus mucosa caused either by infectious or non-infectious agents. Viral URTI is often associated with inflammation of sinus mucosa which may result in obstruction of sinus ostia.[52] The resulting accumulation of fluid in the sinus cavities may lead to proliferation of bacteria resulting in acute bacterial sinusitis.

Viral URTI and bacterial sinusitis may be indistinguishable solely on the basis of clinical features. However, the symptoms of uncomplicated URTI usually completely resolve within two weeks[53] and thus, acute bacterial sinusitis can be diagnosed if symptoms persist without improvement by 10 to 14 days.[54] Sinusitis can also be diagnosed if URTI is associated with more severe symptoms in the first few days: high fever (>38°C), persistant fever, periorbital swelling, facial pain, or dental pain.[55] Purulent nasal discharge is sometimes believed to be an indicator of bacterial sinusitis. However, nasal discharge changes from clear to purulent during the first few days of cold caused by rhinovirus and the colour or characteristics of the nasal discharge do not predict a sinusitis of bacterial origin.[56] Clinical diagnosis of acute bacterial sinusitis strictly requires either prolonged (>10 to 14 days) or severe nonspecific upper respiratory signs and symptoms.[54]

Radiography of sinuses is only moderately helpful in confirming the diagnosis of acute bacterial sinusitis in children since similar findings can also be observed in common cold.[21] In a study of 171 children with nasal discharge, daytime cough or both, lasting from 10 to 30 days, 80% had abnormal maxillary sinus radiograph findings.[57] In children who were diagnosed with acute sinusitis by a strict definition of prolonged symptoms (10 to 30 days) or severe respiratory symptoms associated with abnormal radiographic findings, a bacterial pathogen was recovered from the affected sinuses only from 56% of children.[54]

Wald and colleagues conducted a double-blind, placebo-controlled trial in children to determine the effectiveness of antibiotic treatment for acute sinusitis in children diagnosed by symptoms of 10 to 30 days and radiographic finding. Children treated with antibiotics were more likely to be cured both at 3 days ($p<.01$) and at 10 days

($p<.05$) than children who received placebo. The clinical cure rate at day 10 was 65% for antibiotic compared to 43% for placebo.[57]

Williams et al. conducted a Cochrane review including 7,330 subjects to evaluate antibiotic treatment for acute maxillary sinusitis. They concluded that there were overall moderate benefits of antibiotic treatment in acute maxillary sinusitis.[58]

The overall evidence is in favour of antibiotic treatment in acute bacterial sinusitis. However, diagnosis by strict criteria of prolonged or severe symptoms seems prudent, to curtail a significant amount of antibiotic use. If antibiotic treatment is justified, initial therapy with a narrow-spectrum agent should be a drug of choice in acute bacterial sinusitis.[54]

Otitis media

Otitis media is inflammation of the middle ear, which may be associated with the presence of fluid in the middle ear. The most frequent outpatient use of antibiotics is for otitis media, which accounts for more than 90% of all antibiotic use during the first two years of life.[59] There are two common conditions of otitis media: acute otitis media (AOM) and otitis media with effusion (OME).

AOM is defined as the presence of fluid in the middle ear in association with signs or symptoms of acute local or systemic illness. AOM is generally considered a bacterial infection because a pathogenic bacteria can be isolated from the middle ear fluid in two-thirds of cases of AOM.[60] However, epidemiological surveillance data show a strong association between respiratory virus infections and AOM. Respiratory viruses were detected in nasopharyngeal specimens of 42% of patients with AOM at the time of diagnosis.[19] The percentage of viral isolation might even be an under estimation, because the specimens for viral diagnostics were obtained from 45% of patients after five days of illness, when there has already been maximal virus shedding.[61]

The treatment of acute otitis media (AOM) remains controversial. The rate of antibiotic use for AOM varies from 31% in the Netherlands to 98% in the USA, Australia and New Zealand.[62] Several reviews have assessed the effects of antibiotics in AOM and the result is still not conclusive.

A Cochrane review included six trials from the developed countries with a total of 1,962 children.[63] The trials showed no reduction in pain at 24 hours, but a 34% relative

reduction in pain at 2 to 7 days. However, approximately 85% of the patients settled spontaneously within this time. The authors concluded that antibiotic use provides a small benefit for AOM in children.

Jack Froom et al. reviewed seven randomised blinded trials that compared antimicrobials with placebo in patients with AOM. They concluded that the benefit of routine antimicrobial use for otitis media, judged by short or long-term outcomes, is unproved. The effect of antimicrobials in preventing complications is also uncertain.[64]

However, in a meta-analysis of 33 RCTs, Rosenfeld et al. were in favour of routine antibiotic use for AOM.[65] Although 81% of the AOM with placebo resolved spontaneously by 7-14 days, the authors suggested a modest but significant impact of antibiotics on AOM.

In 1990, the Dutch College of General Practitioners adopted a guideline for the care of AOM. According to the guideline, AOM should be treated with symptomatic treatment (acetaminophen with or without decongestant nasal drops) for the first three days in children aged two years or older. If pain or fever continues for three days, antibiotics may be prescribed for seven days after re-evaluation. In children under two years of age, a mandatory contact with the doctor is advised after 24 hours, when doctors may start antibiotics after re-evaluation.[64]

Although there is no controlled study that has investigated whether the Dutch guideline results in worse outcomes than widely used routine antibiotic practice, Van Buchem et al. conducted a study with 60 general practitioners who treated AOM in 4,860 children aged two years or more with nose drops and analgesics alone. Ninety per cent of children recovered from AOM within the first three days. Only 2.7% of children had a severe course with fever, pain or discharge after 3 to 4 days and only two children developed mastoiditis. The outcomes at two months for these children were similar to those in patients in other countries where routine antibiotic therapy in AOM is universal.[62] The authors were in agreement with Dutch guidelines about the treatment of AOM in children.[66]

OME is defined as the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection.[67] It is commonly a sequel of previous ear infection, which occurs in association with 5-40% of AOM. Meta-analysis of published trials has concluded that antibiotics have limited effects on the short-term resolution of OME.

Longer-term benefit for OME has not been shown.[68,69] The incidence of OME was not different between an antibiotic group and a placebo group when assessed one month after treatment was completed.[69] In another study, the author concluded that about seven children need to be treated with antibiotics for one to have small benefit in OME.[70] In the absence of AOM, antibiotic use is recommended only for the children with both middle-ear effusion and documented hearing loss for three months or longer.[71]

Sore throat/pharyngitis/tonsillitis

Sore throat is another common complaint in children. Most episodes of pharyngitis are caused by viral agents.[72] *Group A streptococci* (GAS) is the most common bacterial cause of pharyngitis, and accounts for only about 15% of all pharyngitis episodes. In a study of children, group A streptococci was isolated from only 12% of patients who had both pharyngeal exudate and fever, whereas viral infection was documented from 31%. Diagnostic testing was not available for rhinovirus and coronavirus, which may have caused infection in other children from whom no etiologic agent was identified.[73] Despite the low incidence of streptococcal sore throats, antibiotics are routinely prescribed for sore throat to relieve symptoms and to prevent complications: otitis media, glomerulonephritis, rheumatic fever.

A review was conducted in 1999 by Del Mar et al. on antibiotics for sore throat including 22 controlled studies with a total of 10,484 cases of sore throat. Antibiotics shortened the duration of symptoms by a mean of only about half a day at Day 3 and by eight hours overall. However, symptoms of half of the untreated patients had also settled by Day 3. Antibiotics reduced the incidence of suppurative complications (acute otitis media and acute sinusitis) and exhibited a protective effect against non-suppurative complications (glomerulonephritis, acute rheumatic fever). However, the incidence of these complications is rare in developed countries. The authors, thus, concluded that protecting sore throat sufferers against suppurative and non-suppurative complications in modern Western society can only be achieved by treating with antibiotics many who will derive no benefit.[74]

Little et al. conducted a RCT of prescribing strategies in managing sore throat with 716 patients aged four years and over. Patients were randomised by types of treatment into three groups: prescription for antibiotics immediately for 10 days, no prescription, prescription for antibiotics if symptoms did not settle after three days. The proportion of

patients better by Day 3 did not differ significantly among the groups. There was also no difference in duration of illness, days off from work or school or proportion of patients satisfied.[75]

The evidence is not conclusive about whether or not to prescribe antibiotics for sore throat. Since the signs and symptoms of pharyngitis associated with viral infection overlap substantially with those of streptococcal pharyngitis, it is difficult to diagnose pharyngitis caused by GAS based on clinical findings alone. However, age is the most important factor in predicting the causative agent of pharyngitis. In a study of febrile exudative tonsillitis, virus was found in 53% of patients younger than six years of age, whereas GAS were found in 46% of children older than six years of age. In fact, none of the children younger than three years of age had GAS.[73] This finding was supported by other studies as well.[76] While the large majority of pharyngitis in children under six is not caused by *Group A streptococci*, empiric antibiotic therapy would result in substantial over-treatment. Therefore, when streptococcal pharyngitis is suspected, appropriate therapy after confirming the etiology by a throat culture may help in reducing inappropriate antibiotic use.[72]

Acute bronchitis

Bronchitis is defined as an inflammation of the bronchial mucosa, resulting in productive cough. It is a self limiting condition most commonly caused by viral pathogens.[22] Viral pathogens such as parainfluenza virus, respiratory syncytial virus and influenza virus account for the majority of agents identified among children with bronchitis.[77]

In practice, physicians commonly prescribe antibiotics for this condition.[78] In a study of 1,398 children who visited a primary care practice with a chief complaint of cough, bronchitis was diagnosed in 33% children and 88% of these children were prescribed an antibiotic.[79] In the National Ambulatory Care Survey in 1989,[80] acute bronchitis was the ninth most common outpatient illness seen by physicians in the United States. In Australia, acute bronchitis is the fifth most common problem encountered by general practitioners.[81]

There are a number of substantial reviews which conclude that antibiotic treatment is not effective in bronchitis, but most of the studies involved adult patients. A meta-analysis by Orr et al. included six randomised controlled trials among adult patients.[82]

Four trials, including the two that were scored highest for methodologic soundness, demonstrated no difference in outcomes achieved by administering antibiotics as compared with placebo. The remaining two trials demonstrated improvement in duration of cough in the group treated by antibiotics.

Another review included eight trials to determine the effectiveness of antibiotics on bronchitis in patients aged above 12 years. Six of the eight trials were included in the review by Orr et al.. The review showed that antibiotic treatment had no effect on the resolution of acute cough.[83]

A Cochrane review[84] included eight randomised controlled trials involving 750 patients aged from eight to over 65. Overall, patients who received antibiotics had slightly better outcome than those who received placebo. However, antibiotic-treated patients reported significantly more adverse effects such as nausea, vomiting, headache, skin rash and vaginitis.

Few studies[85,86] evaluated the use of antibiotics for acute bronchitis in children and none of these studies showed any benefit of antibiotic use for the cough.

2.2.6. Consequences of antibiotic prescribing

"Antibacterial drugs are powerful weapons when used reasonably against infectious targets, but when they are imprudently prescribed for nonspecific symptoms or infection that is probably viral, their use may only contribute to bacterial resistance" (Morton N. Swartz).[87]

The benefits of prescribing antibiotics must be weighed against the costs. Routine prescribing encourages patients' dependence and re-attendance at the surgery, taking up valuable time of the doctor and patient for what is usually a self-limiting condition.[88] Antibiotic treatment in URI is not only ineffective, it may also be harmful. Large numbers of children are unnecessarily exposed to the potential side-effects of antibiotics: allergy, gastric upset, diarrhoea. Unnecessary antibiotic therapy also increases the economic cost of providing medical services. More importantly, routine therapy may delay the diagnosis of serious bacterial diseases. On the other hand, indiscriminate antibiotic use may select for resistant strains of bacteria and may thus lead to more rapid emergence of drug-resistant strains of bacteria.[89,90]

2.3. Antibiotics and Antibiotic-resistance

Knowledge about different antibiotics that are commonly used in children and the mechanism by which they work on bacteria is essential to understand the reality of antibiotic-resistance.

2.3.1. Antibiotics

The term 'antibiotic' was first used to define naturally occurring chemical substances which are produced by various microorganisms and which suppress the growth of bacteria. However, common usage of this term also includes synthetic agents, which were formerly known as antibacterial or antimicrobial agents.

Types of antibiotics

Antibiotics are commonly classified according to their chemical structure. Most antibiotics used in humans can be grouped into few major groups (Table 2.1).

Table 2.1: Commonly used antibiotics in humans

Family	Commonly used antibiotic in humans
Beta lactam	Penicillin, cephalosporin, carbapenem and monobactam
Macrolide	Erythromycin, roxithromycin, azithromycin, clarithromycin
Aminoglycoside	Neomycin, gentamicin, tobramycin, netilmicin, amikacin
Tetracycline	Tetracycline, doxycycline, minocycline
Sulfonomide-trimethoprim	Trimethoprim-sulfamethoxazole, trimethoprim, sulfadiazine
Glycopeptide	Vancomycin

Antibiotics can also be grouped according to their range of activity into a narrow-spectrum, effective against a particular organism only, and a broad-spectrum, effective against many different organisms.

Mechanism of action of antibiotics

Antibiotics suppress the growth of bacteria either by arresting growth and preventing the multiplication of bacteria (bacteriostatic) or by killing the bacteria (bacteriocidal). These exert their bacteriostatic or bactericidal effects in various ways (Table 2.2).

Table 2.2: Mechanism of action of commonly used antibiotics in humans

Mechanism	Family of antibiotics
Inhibits cell wall synthesis	Beta lactam, glycopeptide
Inhibits protein synthesis	Macrolide, aminoglycoside, tetracycline
Inhibits metabolism	Sulfonamide-trimethoprim

Antibiotic use in humans

Antibiotics are used in humans either for treatment or for prevention of infection (prophylaxis). Treatment may be empirical, which means start of therapy pending the results of culture and sensitivity results, or definitive, that is, start of therapy on the basis of culture and sensitivity test. Most antibiotics used for ARIs in children are prescribed empirically.

It would seem that a great deal of empirical therapy in humans around the world is inappropriate. In one estimate, at least half of present antibiotics in United States are prescribed where they are not indicated at all or they are incorrectly prescribed as the wrong drug, the wrong dosage or the wrong duration.[91]

Antibiotics when used for prophylaxis are usually used for a longer period than when used for treatment. Studies showed that administration of even a single antibiotic for two weeks or more leads to the selection of bacteria with resistance, not just to the antibiotic used, but to multiple structurally-unrelated antibiotics.[92] Datta et al. reported a similar finding in fecal *E. coli* specimens collected from women taking prolonged courses of ampicillin for urinary tract infection.[93]

2.3.2. Antibiotic-resistance

The basic principle of antibiotic-resistance is survival of the fittest. Resistance is an adaptive response by microorganisms that enables them to tolerate increasing

concentrations of antibiotics that would normally inhibit them. Antibiotics cannot kill resistant bacteria and thus they survive and multiply, and may cause infection depending on the host's immunity.

Bacterial resistance to antibiotics was observed soon after the introduction of antibacterial drugs. A new antimicrobial era started in the 1930s with the discovery of sulphonamide; sulphonamide-resistant organisms soon emerged, especially among the military population being treated prophylactically with this drug.[94] The golden age of antimicrobial therapy, however, started with the advent of penicillin during the 1940s. Antimicrobials started emerging one after another; but resistance always followed almost immediately after the introduction of each new antibiotic. As a result, only 10 years after the introduction of penicillin in practice, 59% of Staphylococci were reported as resistant to penicillin.[92]

Newer drugs active against bacterial strains were increasingly available during the 1960s to 1980s, but the pace of new antibiotic development has markedly dropped over the 1990s. The problem of antibiotic-resistance has recently become of serious concern as organisms resistant to multiple drugs became widespread, and there is little hope of new antibiotics in the near future.[95-3-5-96-97-98] Common antibiotics are now being reported as ineffective for the treatment of invasive infections caused by resistant organisms.[99-100-101-102] In addition to potentially affecting patient morbidity and mortality, antibiotic-resistance in the community will significantly increase health care costs by increasing the number and duration of hospital admissions and increasing the requirement of higher doses of expensive antibiotics. Thus antibiotic-resistance has become a major public health problem both in Australia and throughout the world.

2.4. Pneumococcal resistance to antibiotics

The first clinical isolate of resistant pneumococcus was isolated in 1967.[103] Between 1967 and 1977, sporadic reports of penicillin-resistant pneumococci were reported from various parts of the world. The next dramatic event in the epidemiology of antibiotic-resistant pneumococci was the outbreak of pneumococcal disease caused by multidrug-resistant strains in South African hospitals in epidemics in 1977. In contrast to the first isolate, which was still susceptible to chloramphenicol, tetracycline, erythromycin, and sulfonamide-trimethoprim drugs, the multidrug-resistant South African strains

recovered in 1977 were shown to have greatly increased minimum inhibitory concentrations to all of these drugs.[104]

2.4.1. Mechanisms of pneumococcal resistance to antibiotics

Resistance to beta lactam antibiotics

Beta lactam antibiotics (e.g. penicillin, cephalosporin) kill pneumococci by binding to PBPs present in the bacterial cell wall. They subsequently interfere with bacterial cell wall synthesis and activate the enzyme amidase, leading to autolysis of bacteria. Six PBPS are found in susceptible strains:1a, 1b, 2x, 2a, 2b, 3. Binding to PBP 2b is essential for the lytic activity of beta lactams on pneumococci.[105] Penicillin-resistant pneumococcal strains have one or more altered PBP that bind penicillin poorly, but are still able to perform their physiological function of cross-linking peptido-glycans. The resistant genes reside in the chromosome and are selected by heavy antibiotic use. Penicillin-resistance requires alteration of at least four distinct genetic elements. Cephalosporin resistance is acquired rapidly, as it needs at most, alteration of two genetic determinants.[106] Highly resistant pneumococci may also acquire different mechanisms of resistance to other unrelated antibiotics. This resistance is transferred by mobile genetic elements such as plasmids and transposons.[105]

Resistance to other antibiotics

Some transposons can cause simultaneous resistance to many different classes of antibiotics. Transposon Tn1545 confers resistance to chloramphenicol, erythromycin, kanamycin, and tetracycline. Erythromycin resistance is due to the gene ermAM, the kanamycin resistance is due to aphA-3, and the tetracycline resistance is due to tetM. Chloramphenicol resistance in pneumococci is due to the production by resistant strains of inducible chloramphenicol acetyltranspherase enzyme. Resistance to tetracyclines and macrolides involves alterations of ribosomal target proteins. Alterations in folate and dihydrofolate metabolism and DNA gyrase structure result in resistance to cotrimoxazole and fluroquinolones respectively.

2.4.2. Factors associated with carriage and spread of antibiotic-resistant pneumococci

Serogroups: Serogroups 6, 14, 19, and 23 are the predominant serogroups of pneumococci manifesting antimicrobial resistance, and account for two-thirds of all

pneumococci isolated during the first two years of life.[107] These serogroups are also commonly identified following antibiotic therapy[107] and are carried for a longer period of time (mean 4.2 months versus 2.7 months for other serogroups; $p<0.01$).[105]

Age: Carriage of, and infection with, resistant pneumococci is mostly associated with young children.[108,109] Barry et al. compared two groups of children with acute otitis media infected with *S. pneumoniae* by controlling for sex, age at first attack and frequency of earlier attacks, and found a higher rate of isolation of penicillin-resistant strains in children under 18 months ($p=.003$).[110] Gratten et al. studied 57 strains of pneumococci isolated from patients with pneumococcal infections in 1978 and found 56% of the isolates from the children were penicillin-insensitive compared to 17% of the isolates from adults.[111] In a multicentre prospective study, Clavo-Sanchez et al. found a significant association of resistance to multiple antibiotics with age younger than five years or older than 65 years.[112]

Hospitalisation: In both children and adults, infection with resistant pneumococci is shown to be associated with hospitalisation.[105] Duration of hospitalisation has been correlated with acquisition of penicillin-resistant strains, with patients colonised by susceptible strains having been hospitalised a median of less than one day and patients carrying resistant strains having been hospitalised a median of 5.5 days.[113]

Day-care centre: Attendance at a day-care centre is a common source of spread of community-acquired resistant pneumococci.[109] Several studies reported a higher level of carriage of resistant pneumococci by children in day-care centres.[114-116] Development and spread of multiply-resistant pneumococci after treatment for acute otitis media have been documented in day-care centres and surrounding communities.[8] A resistant strain acquired by the children from the day-care centre may spread within the family. During the investigation of the first case of a community-acquired multiply-resistant pneumococcus, 27% of children in the same room as the index case were carrying the strain, compared with 11% of older children and staff. Five of 15 family contacts of colonised children acquired the resistant strain, compared with none of 19 contacts of children who did not carry the resistant strain.[109]

Travel: Levy referred to antibiotics as 'societal drugs'-the only class of therapeutics that can affect people around the individual being treated.[117] Bacteria are also social organisms and know no borders. Therefore, the emergence of a resistant strain in one

country is a potential problem in another.[118] This spread became more common with the increasing volume of international travel. Investigators have documented the migration of a strain of multidrug-resistant pneumococcus from Spain to the UK, US, South Africa and elsewhere.[119,120] Strains of penicillin-resistant serotype 23F *S. pneumoniae* isolated from children attending a day-care centre in Cleveland were compared with those from Spain by electrophoretic analysis of PBP profiles and DNA restriction endonuclease cleavage profiles of the PBP 2X and 2B genes amplified with the polymerase chain reaction and by multilocus enzyme electrophoresis. All strains from the two countries were identical by these criteria. The findings demonstrated that the Spanish and Cleveland isolates were clonally related and suggested that the antibiotic-resistant clone of serotype 23F *S. pneumoniae* has spread intercontinentally from Spain to the United States.[120]

Antibiotic use: Exposure to antibiotics may contribute to carriage of resistant strains which may predispose to infection with resistant rather than susceptible strains.[105] The association between antibiotic use and resistance has been documented in both hospital and community settings.[109,121,122] Ecological studies have documented an association between the total amount of penicillin use in a defined area and the isolation of penicillin-resistant pneumococci.[5,122] Among 258 isolates of pneumococci obtained from 232 children, prior therapy with a beta lactam agent had occurred in 56% of patients with penicillin-resistant pneumococcal infections, compared with 14% of randomly selected children with susceptible pneumococcal infections ($P = 0.009$).[123] In a separate study, 65% of the patients infected with resistant pneumococci received antibiotics in the previous three months compared with 17% of controls with susceptible pneumococcal infection.[124] Duration of hospitalisation was not considered in any of the above studies; however, it is possible that exposure to hospital microflora had contributed to the acquisition of the resistant strain. Robins-Browne et al. found that acquisition of penicillin-resistant pneumococci was significantly related to exposure to beta lactam antibiotics even after controlling for young age and duration of hospitalisation.[113] In a case-control study, Amitai and colleagues found that the duration of exposure to beta lactam antibiotics was 13.3 days in patients who had infections with penicillin-resistant pneumococci, compared to 4.2 days in patients with penicillin-susceptible infections ($p<.02$).[125] The association of beta lactam antibiotic use and infection with penicillin-resistant pneumococci was consistent in a separate prospective

study by Clavo-Sanchez et al.[112] Broad-spectrum antibiotics are of particular concern in increasing resistance because they provide selective pressure to increase the number of micoorganisms.

Duration of exposure to antibiotics

Several studies have reported an association between prior antibiotic use and antibiotic-resistance in pneumococci; most of these studies were either ecological or cross-sectional studies. The participants were commonly asked if they received an antibiotic during a given time period before the culture of resistant pneumococci. Type of antibiotic use was sometimes specified; however, most of the time, it was any antibiotic use during that period. The outcome was either penicillin-resistant (PRP) or multiply-resistant pneumococci (MRP).

Table 2.3: Studies that found a positive association between prior antibiotic use in children with pneumococcal resistance to antibiotics

	Type of antibiotic used	Type of resistant pneumoccocci	Duration of study before culture
Tan[126]	Any antibiotic	PRP	1 month
Radetsky[109]	Any antibiotic	MRP	2 months
Reichler[8]	Any antibiotic	MRP	3 months
Deeks[127]	Penicillin	PRP	3 months
Ford[128]	Beta lactam	PRP	3 months
Melander[129]	Any antibiotic	PRP	6 months
Arason[5]	Any antibiotic	PRP and MRP	12 months

Very few studies monitored antibiotic use beyond three months before culture. Even the studies that looked at a longer period of antibiotic use, did not have enough information to specify a definitive period during which antibiotic use was associated with resistance development. However, Brook et al. studied 60 children to determine the effect of prophylactic antibiotic use on the recovery of penicillin-resistant bacteria.[6] Twenty children were receiving amoxicillin and 20 were receiving sulfisoxazole for the prevention of otitis media. The rate of recovery of PRP increased only among patients

who received amoxicillin prophylaxis. The numbers of PRP increased from 0 to 25% during prophylaxis and returned to baseline within 3-5 months after amoxicillin prophylaxis was discontinued.

2.4.3. Prevalence of antibiotic-resistance in pneumococci

Penicillin-resistance

The first penicillin-resistant strain of pneumococcus was isolated from a 25 year old woman patient with hypo-gammaglobulinaemia in Sydney, Australia, who was previously treated with penicillin, tetracycline, erythromycin, chloramphenicol and sulfonamide.[103] This strain was intermediately resistant to penicillin (MIC 0.6 mg/L) and tetracycline (MIC 5 mg/L). Subsequently, resistant strains were identified in New Guinea during a trial of penicillin prophylaxis for pneumonia in 1969.[130] In this trial, a total of 15 isolates were penicillin-resistant and 11 of the 15 isolates were from the group receiving penicillin prophylaxis. However, the first insensitive strain was isolated from a three-year-old boy from the control group, who had suffered from pneumonia five months before and had been treated with penicillin. Subsequently an identical strain was isolated from 14 other people during a period of 14 weeks; all but one of them had recently received penicillin. In 1974, 12% of 518 isolates were penicillin-resistant in New Guinea,[131] and by 1978 one-third of 57 strains isolated from patients with pneumococcal infections were resistant to penicillin.[111] In the United States the first infection due to penicillin-resistant pneumococci was reported in 1974.[132] This resistant strain was isolated from a three-year-old boy with sickle-cell disease. The child developed pneumococcal meningitis which relapsed despite high-dose penicillin therapy. The boy had had several courses of penicillin previously for upper respiratory infections. From 1974 to 1984, penicillin-resistant pneumococcal strains were reported from all over the world.[133]

Erythromycin resistance

The first pneumococcal strain resistant to erythromycin was reported in Canada in 1967 from a 63-year-old man, who was known to have a bronchogenic carcinoma and subsequently developed lung abscess.[134] Pneumococci isolated from the pleural aspirate were resistant to both erythromycin and lincomycin two weeks after starting treatment with oral erythromycin and intrapleural injection of lincomycin. The pneumococcal isolate was sensitive to these antibiotics before starting the treatment. Kislak reported

similar findings in a pneumococcus isolated from the throat culture of a 10-year-old boy, who had received erythromycin and intramuscular lincomycin for treatment of otitis media, one and a half months before this isolation.[135] Erythromycin resistance is common in strains showing multiple resistance.[108] Although multiply-resistant pneumococci are usually characterised by resistance to beta lactam antibiotics in addition to other agents, several case studies reported strains that were susceptible to beta lactam antibiotics but resistant to erythromycin, tetracycline, clindamycin and cotrimoxazole.[136] All three children in the report had a history of prior treatment with antibiotics to which the pneumococci were resistant.

Cotrimoxazole (TMP-SMZ) resistance

A strain of pneumococcus resistant to TMP-SMZ was first identified in 1972 from the sputum of a 58-year-old woman.[137] Klugman et al. reported a pneumococcal strain resistant to this antibiotic isolated from a 20-month-old baby with bacteremic pneumonia, who received cotrimoxazole during the week before isolation of pneumococci.[136] A few other studies also found an association of cotrimoxazole use with subsequent isolation of cotrimoxazole-resistant pneumococci.[138,139] Resistance to TMP-SMZ is associated with multiply-resistant strains isolated from carriers in hospital[108] and also from the healthy children in the community.[140]

Tetracycline resistance

The emergence of tetracycline resistance in pneumococci in the 1960s parallels the widespread use of this antibiotic for the management of acute exacerbations of chronic bronchitis.[105] The first case of tetracycline resistance was isolated from the CSF of a 10-month-old child in Australia in 1963;[141] subsequently an outbreak of tetracycline-resistant pneumococci was detected in a general hospital in the United Kingdom.[142] Five of the ten patients had received tetracycline before the isolation of the resistant strain and all of them either failed to respond to tetracycline or relapsed after temporary improvement. Pneumococcal resistance to tetracycline in Great Britain declined from 12.6% in 1975 to 6.8% in 1976,[105] which may reflect a reduction in the use of tetracycline in that country. Tetracycline use in the United Kingdom dropped from 14.5 million prescriptions in 1969 to 10.1 million prescriptions in 1976.[143]

Chloramphenicol resistance

Chloramphenicol-resistant pneumococci were first identified in Poland in 1970.[144] Pneumococcal strains showing chloramphenicol resistance are usually resistant to other antibiotics, usually including tetracycline and often including penicillin.[105]

Multiple resistance

Multiple resistance is defined in various studies as resistance to at least three different groups of antibiotics.[108] The first multiply-resistant strain was isolated from a three-year-old child in Johannesburg in 1977,[108] who developed pneumonia following repair of a ventricular septal defect. The strain was resistant to penicillin G, erythromycin, clindamycin, tetracycline, chloramphenicol and cotrimoxazole. The child was treated with several courses of penicillin and cephalothin within a month of developing pneumonia. After the recognition of this multiply-resistant pneumococcus, isolate from the children and adult patients and from the staff personnel at the hospital were surveyed for resistant pneumococci. Among the 427 isolates from patients, 51 isolates were multiply-resistant. All carriers of multiply-resistant pneumococci were child patients under three years of age; most of them had received multiple antibiotics for diseases like pneumonia.[108]

Although multiply-resistant pneumococcus was first isolated from South Africa, Spain was subsequently identified as an area with a high prevalence of multiply-resistant pneumococci.[145] The isolation of these strains in both South Africa and Spain was associated with antibiotic use in hospitalised children. Isolation of multiply-resistant strains from a person in Britain following a vacation in Spain suggested the potential for spread of these strains.[146]

2.4.4. Australian perspective of pneumococcal resistance

The prevalence of antibiotic-resistant pneumococci is growing rapidly in Australia. Although pneumococcal resistance to penicillin has been reported more frequently than to other antibiotics, resistance to other antibiotics is also common, sometimes even higher than penicillin-resistance.[4]

The level of penicillin-resistance among *S. pneumoniae* isolates rose from 1.7% in 1989 to 6.7% in 1994 in Australia.[3] This rate of rise in penicillin-resistance in Australia is similar to that seen in Spain in the 1980s and the United States in the 1990s. In the

United States, penicillin-resistant isolates rapidly rose from 1.3% in 1992 to 25% in 1995.[100] However, the rate of penicillin-resistance in 1997 was more than 20%.[4] High-level penicillin-resistance in pneumococci in Australia increased from 0.7% in 1994[3] to 8.6% in 1997.[4]

The resistance rates to erythromycin have also been rising rapidly, an increase from 10.8% in 1994[3] to 16.3% in 1997.[4] The resistance rate to cotrimoxazole in Australia has been consistently high for several years, although it dropped slightly from 42% in 1994[3] to 33.4% in 1997.[4] Resistance to tetracyclines appears to have been steady over the period from 1994 to 1997.[4]

2.4.5. Impact of antibiotic-resistance

The consequences of antibiotic-resistance include increased health care costs for more expensive and powerful drugs, additional hospital days, and on rare occasions, death.[147,148] Morbidity and mortality increase because of delay in effective therapy for specific infections, when resistance emerges to the drug of choice for that particular infection. Resistance may lead to inappropriate empirical treatment which may delay recovery in critically ill patients. Alternative drugs, if they exist, may be more toxic, less effective, or more expensive. Multidrug resistance may lead to some conditions becoming untreatable. For comparison of the effects of infections due to antibiotic-resistant bacteria with those of infections due to antibiotic-susceptible strains of the same bacteria, data were evaluated from 175 published and unpublished reports of investigations of both nosocomial and community-acquired infections with selected bacteria.[149] For both nosocomial and community-acquired infections, the mortality, the likelihood of hospitalisation, and the length of hospital stay were usually at least twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria. Poor outcomes could be attributed both to the expected effects of ineffective antimicrobial therapy, and to the unexpected occurrence of drug-resistant infections complicated by prior antimicrobial therapy for other medical problems.[149] One of the most important consequences of antibiotic-resistance is that resistance can lead to an increase in the incidence of the disease. For example, a person infected with a multidrug-resistant tuberculosis who is not effectively treated may transmit the infection to others.

2.4.6. Confronting antibiotic-resistance

Decreasing unnecessary antibiotic use where it is not indicated, and treating with narrow-spectrum drugs where possible with appropriate doses, could reduce this problem. However, this needs a group effort from physicians, patients, microbiologists, public health officials and pharmaceutical industries. The problem of antibiotic-resistance should be recognised by all sectors and action should be taken to increase awareness in the public. General practitioners acknowledge that a variety of factors influence their prescribing behaviour, which includes patient expectation, workload and questions of litigation.[150,151] There is a widespread misconception among the general public that antibiotics are relatively harmless and can be used in cases of doubt or 'just in case'. Routine prescribing for a viral infection like head cold, chest cold, or sore throat increases the expectation of many patients that antibiotics are the only answers for these infections. A survey of patients' expectations concludes that patients do not usually see the doctor for antibiotics, rather they want a clear explanation and information about the disease.[152] However, it is difficult to explain the disease course, prognosis and treatment within the short period of consultation. Thus, it may be well to shift our attention towards patient education, to empower parents with basic knowledge about respiratory infections, and when antibiotics might help in these infections. This will reduce the number of patient visits to medical practitioners. Physicians will feel more comfortable explaining the reasons for not prescribing antibiotics in situations where they are not indicated. Evidence-based clinical practice guidelines for consumers and physicians might be helpful to reduce the antibiotic overuse if actively promoted and implemented. This new strategy will hopefully reduce antibiotic misuse.

Experts in Australia recommended some guidelines to reduce the prevalence of pneumococcal resistance by reducing inappropriate antibiotic prescribing in children.[106] The guidelines suggest that antibiotics should only be used for specific treatment, not as long-term prophylaxis for otitis media or tonsillitis. They also suggest not treating children with antibiotics for probable viral infections, including non-toxic febrile children without a focus of infection. If an antibiotic is indicated, a narrow-spectrum agent would be preferable.

2.5. Discussion

The higher use of antibiotics in children may lead to higher incidence of carriage of antibiotic-resistant pneumococci among them. Most of the antibiotic use in children is undoubtedly for ARIs. The question is whether antibiotics are of any help in ARIs in children. Many studies have evaluated the effectiveness of antibiotic use on particular types of ARI, for example, sinusitis, otitis media. However, an episode of ARI in children is difficult to categorise to an exclusive type, simply on the basis of clinical signs and symptoms. For example, an episode of ARI which consists of runny nose, fever and earache may simply be a cold episode or an episode of otitis media. Grouping this episode to either of the two categories might create a bias in evaluating an antibiotic's effectiveness. It might therefore be better to examine the effectiveness of an antibiotic by considering all episodes of ARI as a general category, while also categorising them on their degree of severity.

There is enough evidence to suggest an association between antibiotic use and antibiotic-resistance. Most of the studies that have documented this association are observational studies which had the potential to suffer from recall bias. The participants in these studies were commonly asked if they received any antibiotic during a specified period, commonly within the previous one to three months. Therefore, the association suggested in most of the studies is not suggestive of an association between a specific antibiotic use and resistance to that antibiotic. There is also lack of evidence to suggest detailed aspects of the association. Usually the studies considered prior antibiotic use in children for a short period of time, which was usually one to three months. Therefore, the relation of antibiotic-resistance with previous use can only be suggested for a short period of time. Even in studies where data about antibiotic use were gathered for a longer period, information is lacking regarding the specific period during which antibiotics were actually used. As a result, the elapsed time period after antibiotic use up to the development of resistance is not clear. The studies also did not evaluate the required time period for the resistant organisms to become sensitive again. Moreover, no study has yet documented if the duration of antibiotic use, rather than simply any antibiotic use, has an effect on increasing antibiotic-resistance. Although there is a widely held view that broad-spectrum antibiotics are more likely than narrow-spectrum to increase resistance, no study has evaluated this association comprehensively.

Given the fact that antibiotic use in children is associated with carriage of antibiotic-resistant pneumococci and a major portion of antibiotic use in children is for ARIs, we need to know if antibiotic use offers a benefit for these infections. We also need to know if use of the antibiotics that are commonly prescribed to children, for example, beta lactam antibiotics, is associated with carriage of pneumococci resistant to those antibiotics. If there is an association, the amount of exposure needed to develop resistance is also important. We also need to know the dynamics of pneumococcal resistance, for example, time needed to develop resistance after exposure and time needed to return the resistance to baseline. My research hypothesis was developed to reduce the gap in the evidence that less use of beta lactam antibiotics in childrens' respiratory illnesses can reduce the level of penicillin-resistance in pneumococci without compromising clinical care.

Chapter 3 Methods

3.1. Overview

A randomised controlled trial (RCT) of clinical practice guidelines for respiratory infections was conducted in the Australian Capital Territory (ACT), during the period September 1997 to November 1999. This study was part of that trial in which I followed all of the study participants as a cohort for 25 months from September 1997 to September 1999. The overall aim of the trial was to determine if development of clinical practice guidelines (CPGs) for acute respiratory infections could reduce the injudicious use of antibiotics in children. The impact of this intervention is the subject of another thesis by Eileen Wilson. The trial was conducted in a general practice setting involving general practitioners (GPs) and their patients under the age of two years. GPs were recruited and randomly allocated to the early-intervention or the late-intervention group for the purpose of the trial. Children were subsequently recruited by their GPs and were allocated to either of the two groups according to the intervention group status of their GPs. Surveillance of respiratory illness in children was conducted by a daily diary recorded by their parents throughout the trial. Antibiotic-resistance in pneumococci was monitored by collecting four nasal swabs from the children during the study. In this thesis I examine the impact of antibiotic use on respiratory symptoms from the parental diary and pneumococcal resistance in nasal swab isolates.

3.2. Study population

General practitioners and their child patients constituted the study population. General practice is the first point of medical care for any disease; therefore, GP participation was essential to implement guidelines in clinical practice.

We used three eligibility criteria for recruitment of children in the trial. First, children must have been under two years of age at 1 September 1997 and then would be followed for another 27 months. We selected this age group on the basis of evidence that children under five years of age have a higher rate of respiratory infections than older children.[153] Therefore, we expected a higher number of respiratory episodes from these children, which would provide an adequate sample for us to answer the research questions. Secondly, we did not include a child if the parent did not consider the study GP as a regular GP for that child. The reason for selecting this criterion was to measure the effect of guidelines on antibiotic prescribing which would be implemented through the study GP. Thirdly, only one child from a family was considered eligible for the study. By including only one child from a family, we could avoid the influence of family cluster on the child's independence.

3.2.1. Sample size estimation

The project was primarily designed to detect the effect of clinical practice guidelines (CPGs) on antibiotic use for respiratory infections in children. Thus, for estimate of the required sample size, the outcome of interest was days of antibiotic use by children for respiratory infections. To determine the required sample for the study, we accounted for the following: the anticipated rate of respiratory episodes in children; the anticipated days of antibiotic use for respiratory infections in children; the anticipated effect of the intervention; and the impact of the cluster design.

Rate of respiratory episodes in children

The average Australian child under five years of age experiences five to eight respiratory infections in a year.[14] The rate is even higher for younger children. For the purpose of sample size estimation, we anticipated a rate of a minimum five episodes of acute respiratory infection for a child per year.

Number of days of antibiotics

About 60% of all acute respiratory infections in children are treated with an antibiotic.[1] With an average of five days per antibiotic course for 60% of the five respiratory episodes per child-year, we anticipated a minimum 15 days of antibiotic use in children per year for acute respiratory infections.

Effect of intervention

There was no existing evidence which detected an effect of an intervention on antibiotic use. In the absence of evidence, a 20% reduction of antibiotic use was considered clinically worthy of detection. For example, a 20% reduction of 15 days would be 12 days per year of antibiotic use by a child.

Effect of cluster

Children were allocated either to the early-intervention or to the late-intervention group depending on their GPs' group status. This, then, was a cluster design; each cluster being a GP; intervention was implemented through the GPs. For this cluster design, the effect of guidelines on the antibiotic use in a child would provide less information than if randomisation was done by individual children. As a consequence of this cluster design, the outcome of each child cannot be valued as statistically independent. The variation in antibiotic use would be greater among the children cared for by different GPs than it would be among children cared for by the same doctor. In the presence of variation among the GPs, the variance would be different in children between the clusters. For sample size estimation, we anticipated a reasonable variance as 0.5 and a maximum variance as 1.5 between the clusters. The variance of 0.5 means 50% overdispersion as proportional increase in variance between clusters of children. The sample size was calculated in a Poisson distribution model allowing for a cluster effect.

Table 3.1: Estimated sample size for detecting a 20% reduction of antibiotic use in acute respiratory infections in children allowing for cluster design

Variance	GPs	Children	Power
0.5	20	15	92
1	20	15	67
1.5	20	15	50

If the GPs are not very different in antibiotic prescribing, a sample size of 20 GPs and 300 (15/GP) children in each group would be sufficient to detect a 20% difference in antibiotic use for respiratory infections in children, with 80% power at an α level of 0.05. But if there is a massive difference between GPs' prescribing, the sample size would not be sufficient; however, this seemed unduly pessimistic.

Final target sample

According to the calculation and with an anticipation of reasonable variance in GP prescribing, we decided for a target sample of 40 GPs and 600 children for the study.

3.2.2. Sample frame

We obtained two lists of general practices in the ACT, one from the Department of Health and Community Care (DHCC, which is currently known as Department of Health and Aged Care) and the other from the Division of General Practice (DGP). The list obtained from the DHCC consisted of the only practices in the ACT that administered immunisation for children. This list contained names and addresses of the practices, but it did not have the names of GPs working in the practices. On the other hand, the list from the DGP contained the name, address and phone number of their member GPs. We compiled a new list by manually matching the names of GPs with the names of practices based on addresses mentioned in both lists. The new list was cross-checked with the 1997 telephone directory. We then removed the practices from the new list that were not dealing with paediatric patients, such as sports medicine, University health centres and geriatric practices. One hundred and twelve practices remained in the list containing 265 GPs' names, which constituted the sample frame.

The practices were then stratified into solo, small (2-4 GPs) and large (more than 4 GPs) practices according to the number of GPs practising (Table 3.2). We planned to approach one GP from each practice to avoid contamination of information regarding intervention between the early and the late-intervention group. We anticipated that information could be disseminated between the GPs and the patients of the two groups if more than one GP was recruited from the same practice, but allocated to different groups. From a group practice, we randomly selected one GP within the practice by using a random number table. Thus, 112 GPS were identified for potential recruitment.

Table 3.2: List of general practices in the ACT

Type of practice	No. of practices	No. of GPs	% of total GPs
Solo	41	41	15.5
Small	60	158	59.6
Large	11	66	24.9
Total	112	265	100

3.3. Recruitment of study participants

3.3.1. Recruitment of general practitioners

GP recruitment commenced at the end of August 1997. There were three steps in this process. A letter was sent to each of the 112 randomly selected GPs describing an overview of the study. Every GP was then phoned by the chief investigator of the project (RMD) to further describe the purpose of the research and to seek their involvement in the study. If the GP expressed an interest, one of the researchers (DN, EJW) visited the practice. During the visit, the researcher explained in detail the design of the study and their required involvement and also the involvement required from their patients. GPs who agreed to participate in the study signed a consent form at that meeting and were provided a study entry questionnaire (Appendix 3). They were then assigned a random number that classified them either in the early or in the late-intervention group. We developed a computer generated randomisation plan with a block size of ten, which had five zeroes and five ones. We used those numbers to assign

the GPs in either group: zero for the early-intervention and one for the late-intervention group. By the first week of November 1997, we completed the recruitment process for all the GPs contained in the list. However, the number of GPs recruited did not attain the target sample size number. Thus, we started a secondary recruitment in March 1998. We identified eleven GPs from the practices where another GP had been approached before, but had refused to be involved in the study. We repeated the same three steps as performed for the primary recruitment. Although during the recruitment process GPs knew that they could be assigned to either of the two groups, their actual group status was not disclosed to them untill after completing full GP recruitment.

The primary recruitment of GPs was performed between August 1997 and November 1997 and the secondary recruitment during March 1998.

3.3.2. Recruitment of parents and children

Recruitment of parents and children commenced in association with recruitment of GPs. At the time of recruitment, we asked each GP to recruit 15 patients from the practice who were under the age of two years at 1 September 1997. During the GP visit, we also visited the attending receptionists. We explained to them the design of the trial and sought their help in the recruitment of parents and children. We delivered child recruitment sheets and project information sheets to the receptionists(Appendix 3). When a child of under two years visited the GP, the receptionist would attach a recruitment sheet and an information sheet with the case note. During the consultation, the GP would explain briefly the trial and his or her involvement in the trial to the parent. If a parent agreed the GP would immediately send the name and telephone number of the parents to the researchers by fax or post. One of the researchers (EJW, DN) then contacted the parent by telephone and confirmed that the child met the eligibility criteria. If the child was eligible to participate, we explained the required involvement of the parent and the child for the project. If the parent expressed an interest in receiving more information about the project, we sent a package to the parent which contained a consent form, a study entry questionnaire, a diary for the first month and a refrigerator magnet with the ARIC study logo to secure the diary in a noticeable place (Appendix 3). A sample diary and an instruction sheet were also included in the first package to help the parent in filling out the diary (Appendix 3). Children were

automatically assigned to the early or late-intervention group according to the group status of their GPs. The GPs continued the recruitment process unless we asked them to stop recruitment after 15 parents agreed to participate.

Recruitment of children continued from September 1997 to April 1998.

3.4. Intervention by clinical practice guidelines (CPGs)

3.4.1. Objective

The objective of the intervention was to reduce antibiotic use for acute respiratory infections in children.

3.4.2. Development of CPGs

The GPs and a group of parents from the early-intervention group were actively involved in the development of clinical practice guidelines. The process of development of CPGs began with a parent focus group in November 1997. Information from the parent focus group was subsequently presented to a meeting with GPs. After six interactive sessions with GPs and parents, the clinical practice guidelines for parents and GPs were developed in April 1998 (Appendix 3).

3.4.3. Implementation of intervention

During May 1998, we provided clinical practice guidelines to all the GPs and parents of the early-intervention group. The guidelines were introduced to the participants of the late-intervention group in February 1999.

3.5. Data collection

Data collection commenced with recruitment of the study participants. GPs and parents filled in a study entry questionnaire at the time of recruitment. This questionnaire provided information about the demographic details of the participants as well as past experience of participants in caring for ARI in children. A daily respiratory diary was employed to collect data on respiratory infections and treatment in children. These diaries were recorded by the parents and returned to us every month, which allowed us a prospective data collection. A nasal swab was collected from the children four times during the study to monitor the pneumococcal carriage and pneumococcal resistance to antibiotics.

3.5.1. GP questionnaire

The GP questionnaire was developed using a range of sources including a questionnaire previously used in a study in Adelaide (personal communication with RMD). The modified questionnaire was divided into four sections (Appendix 3):

Section A: socio-demographic information about the GP.

Section B: information regarding medical practice and involvement in different medical associations.

Section C: information regarding clinical practice in treating acute respiratory infections.

Section D: attitudes of GP towards clinical practice guidelines.

3.5.2. Parent questionnaire

The parent questionnaire was developed on the basis of the questionnaire used in a previous study in Adelaide (personal communication with RMD). This questionnaire was divided three sections (Appendix 3):

Section A: socio-demographic information about the child.

Section B: management of acute respiratory infections by the parent.

Part C: parents' satisfaction with GP visit for their child.

3.5.3. Respiratory diary

We developed a respiratory diary in a monthly calendar format, which was similar to the diary used by Roberts.[154] Parents were supplied with an example-filled diary in the recruitment package to help them in properly recording the daily diary. The diary allowed parents to record symptoms of respiratory infections in children and treatment use by the children (Appendix 3).

3.6. Outcome

3.6.1. Surveillance of respiratory illness and its management

Data from the respiratory diary were used for surveillance of respiratory illnesses and management of the illnesses. In the diary, parents recorded symptoms of respiratory illness and details of management of illness including antibiotic use and health service utilisation. At the end of each month they sent the diary back to the research office. To obtain the best possible data, we immediately checked the information on receipt. If we found any incomplete information in a diary, we rang the parent for clarification. In the middle of each month, a research assistant rang the parents who did not send diaries for the previous month. Sometimes she also completed diaries over the telephone for the parents who were unable to fill the diary for a month.

Data derived from the respiratory diaries were:

1. Symptoms of respiratory illness including runny nose, blocked nose, green nasal discharge, dry cough, moist cough, wheeze, sore throat, hoarse voice, earache, ear discharge, fever and cold.

2. Health service utilisation including doctor or hospital visit, hospital admission with the reason.

3. Medication used including duration of use.

4. Any other illness.

On the basis of parents' reporting of a respiratory illness I defined a respiratory episode. An episode was defined as the occurrence of at least two consecutive days of any of the 12 symptoms: runny nose, blocked nose, green nasal discharge, dry cough, moist cough, wheeze, sore throat, hoarse voice, earache, ear discharge, fever and cold. The end of an episode was defined as the occurrence of at least two symptom-free days. This approach

to definition of a respiratory episode has previously been used by Samet et al. in a study of nitrogen dioxide and respiratory illness in infants.[155] Samet used five symptoms to define a respiratory episode which included runny or stuffy nose, dry cough, wet cough, wheeze or trouble breathing. I included another five symptoms and signs (green discharge, earache, ear discharge, sore throat, hoarse voice) to define an episode because of their frequent occurrence in children in association with respiratory illnesses.

3.6.2. Surveillance of pneumococcal carriage and antibiotic-resistance in pneumococci

We collected a nasal swab from each child four times during the 25 months of the study period to determine the carriage rate of pneumococci and to monitor the level of antibiotic-resistance to pneumococci. To monitor the change of carriage and resistance over the study period, we planned to collect two swabs per year for the two years of the study at approximately the same seasonal period. Thus, the first and third set of nasal swabs were collected during autumn (March and April) 1998 and 1999 respectively and the second and fourth swabs were collected during winter (August and September) 1998 and 1999 respectively. These particular periods were chosen to determine the carriage rate of pneumococcus before and after winter, as it was expected that children would have more respiratory episodes and more antibiotic prescriptions during winter. The procedure of the nasal swab collection is detailed in the appendix 3.

Laboratory procedure

The laboratory procedures were undertaken in the Canberra Hospital Microbiology Department. Collected specimens were immediately inoculated onto blood agar plates and incubated for 18-24 hours at 35 degrees in an atmosphere with added 5% CO_2. The media used were standard horse blood agar (HBA), standard horse blood agar with added 5 mg/L gentamicin (HBAG) and Mueller Hinton agar with 5% defibrinated sheep blood (MHASB). The media were prepared according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.

Isolation of Pneumococci: The medium used in the primary plates was HBAG. Suspicious colonies were selected from the primary plates and subcultured onto HBA for pure growth, with an optochin disc placed between the first and second streak lines in order to detect pneumococci. These subcultured plates were incubated for 18-24

hours at 35 degrees C in an atmosphere with added 5% CO_2. Suspicious colonies were those with the typical morphology of pneumococcus on blood agar. Small pneumococcal colonies are smooth, transparent and low convex while larger colonies become flattened or depressed centrally, showing the 'draughtsman form'. A partial clearing of blood and a greenish discolouration (α haemolysis) was produced underneath and in a narrow zone around the colonies. Primary plates with no suspicious colonies were also re-incubated in the same environment for the same duration. Isolates from secondary plates, which showed typical morphology of pneumococci and were sensitive to optochin, were frozen and stored for sensitivity testing by using Protect Beads. Organisms which showed atypical morphology and were resistant to optochin disc were discarded. Primary plates which developed suspicious colonies after 48 hours were subcultured for purity on HBA with an optochin disc and were incubated for reading the next day. The rest of the primary plates were discarded. On the third day, if the secondary plates showed typical morphology and sensitivity to optochin, those were stored with Protect Beads. Colonies which showed typical morphology, but resistance to optochin, were further tested by bile solubility test. Only the predominant colony of each isolate was tested for sensitivity to antibiotics.

Sensitivity testing: Sensitivity testing was performed on isolates shown to be *S. pneumoniae*. One predominant colony for each isolate was selected to test. The following antibiotics were chosen for disc susceptibility testing: oxacillin, erythromycin, cotrimoxazole, tetracycline, chloramphenicol and cefotaxime. Susceptibility testing was performed on Mueller Hinton Agar with 5% defibrinated sheep blood (MHASB) and according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Plates were predried in air at 35 degrees C for 20-30 minutes before use. A bacterial suspension was prepared from the culture plates into Mueller Hinton broth or 0.9% saline, at a turbidity equivalent to a 0.5 McFarland standard. Plates were inoculated with bacterial suspension within 15 minutes of adjustment. A sterile swab was then dipped into the suspension, squeezed against the side of the tube to get rid of excess inoculum, then swabbed over the surface of the plate, making sure all sides of the swab touched all parts of the plates. After allowing the swabbed plate five minutes to dry, discs were placed on the plates. According to NCCLS guidelines, a maximum of four discs were placed on a 100 mm plate. Discs were pressed down onto the agar surface to ensure complete contact. Plates were inverted and incubated within 15

minutes of disc placement. Laboratory reference strains *S. pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 25923 were used as controls.

Minimum inhibitory concentrations (MICs) for penicillin and erythromycin by E-strips were also tested for each isolate. Sensitivity to cefotaxime was also tested using E-strips, but only for the isolates that were resistant to penicillin. The E-test consisted of strips, which were impregnated with gradients of varying antibiotics. The Minimum Inhibitory Concentration (MIC) was read where the 'inhibition ellipse' intersected the scale of the strip and was always at the point of complete inhibition of growth. Interpretation of the ellipse was as follows:

If the ellipse came into the scale between dilutions, the upper dilution was read as the MIC.

If the ellipse came in unevenly at different intersections, the upper dilution was taken as the MIC.

If there was any macro colony present, the MIC was read where it was completely inhibited on the scale.

If there was a double zone, the higher dilution was taken as the MIC.

If the ellipse suddenly dropped off near the strip, the MIC was determined by reading through the curve of the ellipse.

Interpretation of sensitivity test

The MIC breakpoints published by NCCLS Guidelines were used to define the isolate as sensitive to penicillin when minimal inhibitory concentration (MIC) was less than or equal to 0.064 mg/L, intermediate resistant when MIC was greater than 0.064 mg/L but less than or equal to 1 mg/L, and highly resistant when MIC was greater than 1 mg/L. All isolates were tested for cefotaxime susceptibility with a 30 µg disc and only the penicillin-resistant isolates were tested with an E-strip for cefotaxime MIC.

Antibiotic-resistance was categorised as either intermediate or high level resistance. Multi-drug resistance was defined as the presence of intermediate or high level resistance to two or more antibiotics.

The following table was made from NCCLS tables 2C, 3 and 3C; it was used for determining sensitivity patterns of *S. pneumoniae*, along with quality-control values.

Table 3.3: Zone sizes for antibiotics tested against *S. pneumoniae*

Antibiotic	Disc content	Zone diameter			ATCC 49619	ATCC 25923
	(μg)	R	I	S	Zone	Zone
Cefotaxime	30					25-31
Chloramphenicol	30	≤ 20		≥ 21	23-27	19-26
Cotrimoxazole	1.25/23.75	≤ 15	16-18	≥ 19	22-27	24-32
Erythromycin	15	≤ 15	16-20	≥ 21	25-30	22-30
Oxacillin	1			≥ 20	24-30	18-24
Tetracycline	30	≤ 18	19-22	≥ 23	27-31	24-30

There were no data for cefotaxime as third-generation cephalosporins are usually extrapolated from oxacillin zone size and penicillin MIC value.

Table 3.4: MIC values for *S. pneumoniae* against erythromycin and penicillin (NCCLS tables 2C and 3C)

Antibiotic	MIC (μg/ml)			ATCC 49619
	S	I	R	Range
Erythromycin	≤ 0.25	0.5	≥ 1.0	0.03-0.12
Penicillin	≤ 0.06	0.12-1.0	≥ 2	0.25-1.0

3.7. Data management

A database was established in Microsoft Access software. The database contained fields for the diary, questionnaire, and tracking forms to track every datum received from the participants. Each time we received a diary the date was immediately noted in the tracking form of the database. After the end of each month we made a list of the parents who did not send the diary of that month. We recruited a research assistant who reminded the parents at the middle of the following month to send the diary at the earliest possible time.

Every month we sent birthday cards to the children whose birthdays were in that month (Appendix 3). It seemed encouraging to the parents, as sometimes parents reminded us in the diary that the next particular date was the child's birthday. We also sent seasons'

greetings and Christmas wishes to the children and parents. We sent regular newsletters to parents and GPs informing them of different aspects of the study (Appendix 3).

During each set of nasal swab collections, a research assistant and I rang every parent to remind them on the evening before the date of swab collection. During that telephone reminder we also asked parents about any confusion or any problem regarding the study. That conversation helped both parents and researchers to know each other and also helped parents to feel involved in the study; it also helped us to track the changes of address and telephone number for parents.

Most of the data were entered into the database by a professional data-entry firm and data about nasal swab collections were entered into Excel 4 by a research assistant in Canberra Hospital Pathology.

3.8. Analysis

I exported data from Microsoft Access to SPSS by using Excel-4. I then performed descriptive analysis by using SPSS 7.5 for Windows. However, for multivariate analysis, I transported the data from SPSS to Stata by using Stata transfer. I created graphs using Microsoft Excel.

3.8.1. Respiratory illness and antibiotic use

Crude rates were calculated for respiratory symptoms, respiratory episodes and antibiotic use for all children. Total observation days for a child in the study were used as a denominator in defining the rate. The period of observation for children was based on the daily diary returned by parents. In fact, the day of diary record was taken as the day of observation for a child.

An episode was defined as the occurrence of at least two consecutive days of any of the 12 reported symptoms in the diary; the end of an episode was defined as the occurrence of at least two symptom-free days. Duration of an episode was calculated from the onset of symptoms to the last day on which symptoms occurred before the occurrence of two symptom-free days.

The 12 symptoms and signs were grouped into four major groups depending on their association with the specific illnesses: ear symptoms, throat symptoms, lower respiratory and upper respiratory symptoms. Ear symptoms included earache and ear discharge; throat symptoms were sore throat and hoarse voice. Moist cough and wheeze

constituted lower respiratory symptoms and runny nose, blocked nose, green nasal discharge, dry cough and 'cold' were included as upper respiratory symptoms.

The episodes were classified into five types depending on the type of symptoms present in the episode. The types were: ear episode, throat episode, lower respiratory, upper respiratory and fever episodes.

The rate of a specific symptom for a child was calculated by dividing the total number of days of that symptom in the children by the total number of days of observation for children in a year. The episode rate, the rate of total and each specific antibiotic use were also calculated in the same way.

I used multivariate modelling in Stata to test the effect of antibiotic use on the severity of respiratory episodes. The outcome of severity was measured as the average number of symptoms per day from the point of doctor visit up to the end of the episode. The data used for this variable were continuous-type. I anticipated that the episode of a child might not be independent of other episodes in the same child; I therefore used a random effect linear regression model that allowed adjustment for the impact of clustering within child. My goal was to obtain a valid estimate of the effect of exposure to antibiotic use on the severity of respiratory episodes after controlling for potentially confounding factors. I followed the stages to develop a multivariate model suggested by Kleinbaum, where the stages are variable specification, interaction assessment and assessment of confounding.[156]

Variable specification

I selected potentially confounding variables that could be biologically associated with respiratory illness or that had been shown in previous studies to be related to respiratory illness. As the severity was measured from symptoms reported by the parents, I also considered the factors that could influence parents' reporting of severity. The variables were selected from the diaries and the questionnaires completed by parents and GPs. The details of the modelling strategy and the final model accepted are provided in Chapter 7.

Adjustment for clustering

The episodes experienced by the same child cannot be regarded as independent regarding the severity of illness. By using a random effect linear regression model I

made a robust estimate of coefficient and standard errors. The robust estimator relaxes the assumption of independence of the observations by producing corrected standard errors for correlated observations within child.

The command I used in STATA for linear regression to determine the effect of single exposure of antibiotic use on the severity of respiratory episode was:

regress severity antibiotic, cl(idno)

severity=logarithm of average number of symptoms per day after the doctor visit up to the end of the episode

antibiotic=episode associated with antibiotic use

cl(idno)=clustered by child identification number (adjust for multiple episodes from the same child)

3.8.2. Antibiotic-resistance and antibiotic use

Pneumococcal carriage was monitored in children by collecting a nasal swab four times during the 25 months of study as described above. The descriptive analysis of pneumococcal carriage and resistance to six antibiotics during four collections is presented in Chapter 5.

To detect the effect of antibiotic use on antibiotic-resistance, I limited my analysis to beta lactam antibiotic use and its effect on penicillin-resistance in pneumococci. I analysed the data using a multiple logistic regression model in Stata that adjusted for cluster effect within child. I started modelling with specification of the variables, followed by interaction assessment and completed with confounding assessment. The details of the modelling strategy and the final model are presented in Chapter 6.

3.9. Ethics

The Ethics Committee of the Australian National University approved the trial. Nasal swab collection was approved separately by the Ethics in Human Experimentation Committee. We informed the GPs and the parents of the children about the details of the trial by providing an information sheet at recruitment (Appendix 3). Written consent was obtained from each of them during recruitment (Appendix 3). In the consent form, it was made clear to the participants that they would be free to withdraw at any stage of the study and the information about them would be kept confidential. Confidentiality

was maintained by using a unique identification numbering system for each child and each GP.

3.10. Pilot studies

We did not pilot the diary and the questionnaires used in the study as they had been used in previous studies.

3.10.1. Piloting the process of intervention

During June 1997, we arranged a meeting with a group of GPs and a meeting with a group of parents to pilot the process of intervention. The pilot studies are described by Eileen Wilson in her thesis.

3.10.2. Piloting nasal swab collection

In March 1998, the surgery of a study GP was used as a pilot site for nasal swab collections from children. The objective was to test the swab stick, agar plate and collection technique. A total of nine child patients of that GP and their parents participated in this pilot. Three research assistants were involved in swab collection. They were practically taught the procedure of swab collection and the process of inoculation on agar plate by a laboratory scientist from Canberra Hospital Pathology. The swab collectors alternately collected a swab. The swabs collected by each collector were kept separated.

The procedure of swab collection and the size of swab stick seemed quite acceptable to the children, as well as to their parents. A pneumococcus was isolated from 30% of the swabs as was expected, which proved that the agar plates were satisfactory. There was no difference of result among the swabs collected by three collectors.

3.11. Discussion

Although my part of the project treated the children as a prospective cohort, the study was also designed as a randomised controlled trial, which itself minimised a number of potential problems associated with other study designs. We considered the impact of clustering in sample size calculation and also in methods of analysis. The process of random selection of the GPs was designed to maximise generalisability and was also intended to eliminate the chance of contamination of information between two intervention groups. Although this would not create a problem for the pneumococcal

resistance study, it could have resulted in a reporting bias by parents, which would definitely affect the analysis of severity of respiratory illness in the cohort.

Loss to follow-up is the biggest problem for any study of such long duration. We undertook a number of strategies to maintain a good participation rate as outlined above. A research assistant rang the parents every month to remind them about the previous month's diary. She also filled in diaries for the parents who claimed not to have received a diary for that month or failed for some other reason to return the diary. We regularly sent birthday cards for children, and seasonal greetings to the children and the parents. We also sent regular newsletters to the parents informing them of the progress of the study and expressing appreciation of their enthusiastic participation. A reminder call before each swab collection also helped in enhancing a sense of involvement in the parents to the study.

We also sent regular newsletters to the GPs informing them of different aspects and progress of the study, and posted them the most current evidence-based information regarding the management of ARIs in children. Information regarding antibiotic-resistance from international conferences was also part of the newsletters.

The study design had a few limitations.

Limitations in GP recruitment: The majority of the study GPs (58/63) were recruited strictly by a random process in primary recruitment, which we could not maintain during secondary recruitment. During primary recruitment, we approached only one GP from a practice in the sample frame. We anticipated that 15 children would easily be recruited by each GP within two months. Although some of the GPs could recruit 15 children in a week, in reality most of the GPs were not able to recruit even half of the expected number of children even after six months in the study. At this stage, we thought about the feasibility of recruiting more children from the GPs who completed recruitment first. However, because of the GP-cluster effect, even a large number of children from one GP would not have greatly enhanced the power of the RCT part of the study. We therefore decided to approach some more GPs, which would be likely to increase the power by increasing clusters as well as the total number of children. However, during primary recruitment, we had approached one GP from each of the practices in the sample frame. We therefore selected a few additional names of GPs from the list of practices. These selected GPs were practising in group practices where another GP had

been approached before, but where that GP had declined to participate. This subset of additional GP recruitment could lead to selection bias of the GP sample. However, as with the primary group, we randomly allocated them to the early or late-intervention group.

Problems in child recruitment: The recruitment of children took much longer than anticipated. We expected two weeks to be enough time to recruit 15 children from a GP's surgery. However, even after repeated reminders and encouragement from us, it took several months for most of the GPs to recruit even half of the children. One of the reasons for this slow recruitment was the timing of recruitment. We started recruitment of study participants in late September, when rates of colds and coughs are declining. These symptoms are usually the main reasons for GP visits for children.

Apart from that, even after we provided a written recruitment protocol and several reminders, a few GPs misunderstood the first step of the recruitment process. They approached only the children who visited them for some sort of respiratory infection.

During the Christmas and summer holiday in December-January 1998, the recruitment became even slower; it was very difficult to contact parents during that period. At that point, the number of recruited children was far below the estimated target. We sent a letter to all study GPs asking them to continue to recruit more patients over the next two months. A few GPs asked if they could select children from their patient lists rather than waiting for children to visit surgeries, which seemed to be the easier and quicker way to recruit the required children. We agreed with them at that point and offered the same strategy to other GPs as well. We also offered assistance in selecting patients from the list. During March 1998, the number of children increased because a good number of children were recruited by the secondary recruitment of GPs. It took the general practitioners eight months to recruit 502 children in the study, whereas we had hoped to get 600 children within the first few weeks.

The prolonged recruitment also partly resulted from the workload in general practice. GPs were asked to approach the parents of every child under two years of age, who came to visit them. In reality, GPs did not always maintain the recommended criteria for children recruitment. A few GPs selected patients from their practice lists rather than approaching all subsequent eligible patients in the surgery. GPs might have selected parents whom they considered competent to maintain diaries for a long study

period. GPs also excluded parents who could not speak English well, as they anticipated problems in recording diaries. This eliminated an opportunity to see whether a cultural difference could make a difference in management of respiratory infections. We also received some names from GPs of children who were not their regular patients. We could control this problem by asking parents whether they considered the GP as the child's regular GP. Overall, the selection of children probably resulted in a bias in the sample, as we observed a social and educational profile of the families in the study compared to average Australian families.

In retrospect, I think it would have been easier and quicker to recruit the sample if the receptionists had been given the primary responsibility, to attach the recruitment sheet to the case history of each successive eligible child. Alternatively, a research assistant could have been involved with each GP for a certain period to establish adequate recruitment. We were dependent however on the goodwill of GPs, who were somewhat idiosyncratic in their approach to recruitment.

The setting of the study itself introduced some limitations. The people of the ACT are different from average Australians in respect to their higher level of education and income. Higher socio-economic status might influence the incidence of illness, health care utilisation and antibiotic use. Most of the children in the study were in families where both parents were working: this might affect their management strategy for children's respiratory infection. The GPs in the ACT are frequently involved in research which could result in a difference in their treatment strategy from their counterparts in other parts of Australia.

3.11.1. Effect of the limitations on the issues explored in this thesis

We would have preferred a fully random sample of GPs and patients for this project. Lack of randomness could compromise the generalisability to the Australian population as a whole of the findings. Nevertheless the questions that are explored in this study remain relevant and pertinent to the recruited population and the growing body of knowledge on the issue of antibiotic use in the Australian population.

Chapter 4 Results: The cohort

4.1. Overview

This chapter describes the details of the enrolment process and the baseline characteristics of study participants. General practitioners (GPs) and a group of children from their practices participated in the study. The characteristics of the study participants are based on the analysis of study entry questionnaires completed by the GPs and parents at recruitment. I also describe the dynamics of the cohort with the rate of diary return for every month, and loss to follow-up.

4.2. Recruitment of study participants

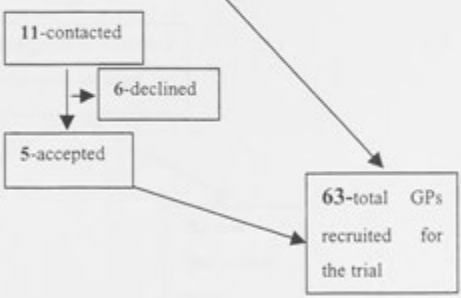
4.2.1. GP recruitment

Recruitment of GPs took six months, from September 1997 to February 1998. Details of the recruitment procedure were described in Chapter 3. Of the 112 eligible GPs from the original list, seven GPs were not able to be contacted at the address given. We contacted 11 more GPs at the later stage of recruitment. Thus we approached a total of 116 GPs from the ACT, and 63 (54%) participated. The results of GP recruitment are shown in Figure 4.1.

Figure 4.1: GP recruitment

A. Primary recruitment

B. Secondary recruitment

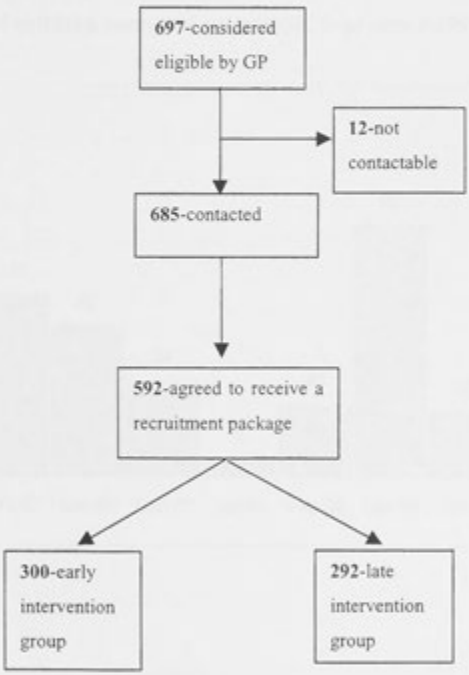


We randomly allocated 31 GPs to the early-intervention group and 32 GPs to the late-intervention group.

4.2.2. Recruitment of children

Recruitment of children was conducted from September 1997 to April 1998. We received a total of 728 recruitment forms back from the GPs with the name and contact number of the parents: 697 were considered eligible by the GPs. The eligibility criteria of children have been described in Chapter 3. Of the 697 parents, we could not contact 12 because of disconnected or wrong telephone numbers. Parents of a total of 592/697 (86%) children agreed to participate in this trial (Figure 4.2).

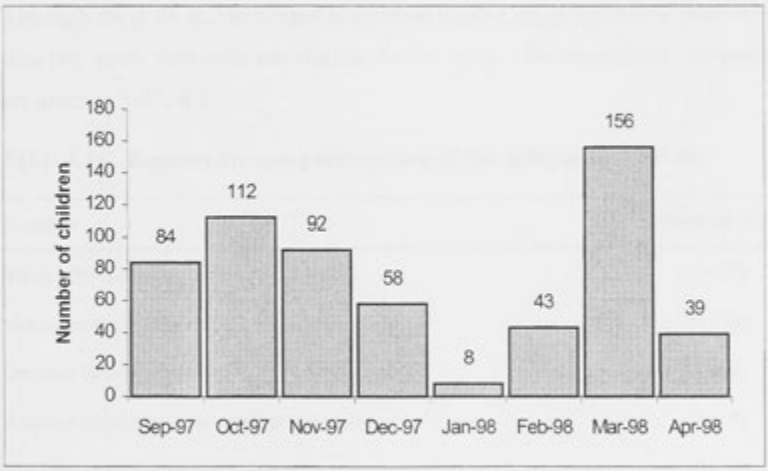
Figure 4.2: Recruitment of study children



Rate of recruitment of children per month

Recruitment of children began in September 1997 and continued to April 1998. During the Christmas and New Year holiday in December1997 and January 1998, the recruitment process was very slow because of unavailability of the parents. At that time the number of recruited children was far below the estimated target. At that time, we sent a letter to all study GPs asking them to recruit more patients within a month or two. We also offered assistance in the recruitment process by providing a research assistant for the surgery if needed. During March 1998, the recruitment rate improved because of the large number of patients recruited by the second recruitment of GPs. The whole process of recruitment was completed by the first week of April 1998.

Figure 4.3: Number of children recruited per month, September 1997-April 1998



4.3. Non-participants

4.3.1. Reasons for non-participation of GPs

It was difficult to determine the reason for non-participation of the 33 GPs who refused to be contacted by a researcher. Twenty GPs declined to participate in the study after a meeting with a researcher. They offered one or all three of the following reasons:

1. Inadequate number of child patients.
2. Lack of time, already involved in other studies.
3. Lack of interest in the study.

4.3.2. Reasons for non-participation of children

Of the 685 parents of the children contacted, 93 (14%) did not participate in the study. Although these 93 children were considered eligible by GPs, three of them were older than two years, thus were not eligible for the study. The reasons for non-participation are given in Table 4.1.

Table 4.1: Reasons for non-participation of the children in the trial

Reasons	Number (%)
Study GP was not the primary GP	27 (29)
Not interested in the study	24 (26)
Decided to move from ACT	17 (18)
Another sibling was recruited in the study	12 (13)
Time pressure for record keeping	10 (11)
Child older than 2 years (not eligible for the study)	3 (3)
Total	93 (100)

4.4. Active participants

Nine of the 63 recruited GPs had withdrawn from the study before the completion of the total recruitment process in April 1998; 7 of them were from the intervention group. Eight of the nine GPs gave inadequate numbers of child patients in the practice as a reason for withdrawing from the study. One GP, who suddenly decided to retire, had recruited only one patient for the trial.

Of the 592 parents who agreed over the telephone to receive a recruitment package, 90 did not reply when the package was sent.

At the end of recruitment in April 1998, 54 GPs and 502 children remained active in the study. Of the 54 GPs, 24 were in the early-intervention arm and 30 in the late-intervention group. Among the 502 active children, 257 were recruited by the GPs of the early-intervention group and 245 by the GPs of the late-intervention group. 28 GPs recruited 10 or more patients, 15 recruited 6-9 patients and 11 had 5 or less.

4.5. Baseline characteristics

4.5.1. GP characteristics

Fifty-two of the 54 active GPs (96%) sent a study entry questionnaire back to us; 58% of them were male. Half of the GPs had graduated from medical school after 1977, three of them had graduated between 1987 and 1995. The average period of clinical practice for the GPs was 16 years (standard deviation 8, range 1-33 years). Most of the GPs (75%) worked in a group practice. Half of the GPs work 40 hours per week in the surgery. The GPs spent an average of 3.5 hours per week (standard deviation 3, range 1-15 hours) in reading background materials. All the study-GPs were vocationally registered. The vocational training program is conducted by the Royal Australian College of General Practitioners to prepare the medical graduates for entry into unsupervised general practice. Most of the GPs (92%) in the study were members of the ACT Division of General Practice either alone or in conjunction with RACGP, AMA and other medical associations.

Most of the GPs (77%) who worked in solo practices were male, whereas the sex ratio was equal in group practices. Among the GPs who worked part-time (<=30 hours/week), 75% were female. Male GPs worked significantly longer in the surgery than the female GPs (90% of male GPs worked more than 30 hours per week compared to 59% of the female GPs, p=.009). The characteristics of study GPs are tabulated in Table 4.2.

Table 4.2: Characteristics of general practitioners (n=52)

Characteristics (Number of respondents)	Number (%)
Sex (52)	
Male	30 (58)
Female	22 (42)
Year of graduation (52)	
Before 1972	13 (25)
1973-1977	11 (21)
1978-1982	15 (29)
After 1982	13 (25)
Years of clinical practice (51)	
<12 years	15 (29)
12-15 years	12 (23.5)
16-21 years	11 (22)
>21 years	13 (25.5)
Number of GPs per practice (52)	
1 GP	13 (25)
2-3 GPs	28 (54)
>3 GPs	11 (21)
Hours in the surgery per week (52)	
1-30 hours	12 (23)
31-40 hours	16 (31)
41-45 hours	11 (21)
>45 hours	13 (25)
Hours of background reading/week (51)	
2 hours	28 (55)
>2 hours	23 (45)

4.5.2. Characteristics of children

477 of 502 (95%) parents of the participating children returned the study entry questionnaire. These questionnaires contained demographic, environmental and health-related information about the children.

The mean age of the children at recruitment was 11.8 months with a range from two weeks to two years. Thirty-five per cent of the children were the only child of their parents during recruitment and another 40% had only one sibling. Most of the children were breastfed for at least some time and 26 children were being breastfed at study entry. The mean duration of breastfeeding at that point was seven months with standard deviation of 5.5 months. Half of the children were breastfed for more than six months. The characteristics of the children are shown in Table 4.3.

Table 4.3: Characteristics of children at recruitment (n=477)

Characteristics (number of respondents)	Number (%)
Age (476)	Mean 11.8 months, range 2 wks-2 yrs
Sex (477)	
Male	217 (45.5)
Female	260 (54.5)
Number of siblings (474)	
No sibling	166 (35)
1 or more siblings	308 (65)
Ever breastfed (460)	
Never	37 (8)
Breastfed	423 (92)
Immunisation for the age (468)	
Not immunised	18 (4)
Immunised	450 (96)
Types of day-care (472)	
Care by parents	283 (60)
Private care by Nanny or a relative	38 (8)
Family day-care	27 (6)
Day-care centre	124 (26)
Duration of day-care per week (472)	
No day-care	283 (60)
1-20 hours	79 (17)
21-40 hours	73 (15)
>40 hours	36 (8)
Any major illness (472)	
No	396 (84)
Yes	76 (16)

4.5.3. Characteristics of parents

Over 30% of the parents in the study had either a graduate or a postgraduate degree from university. Thirty-five per cent of parents earned more than A$60,000 per annum. The characteristics of parents and family are tabulated in Table 4.4.

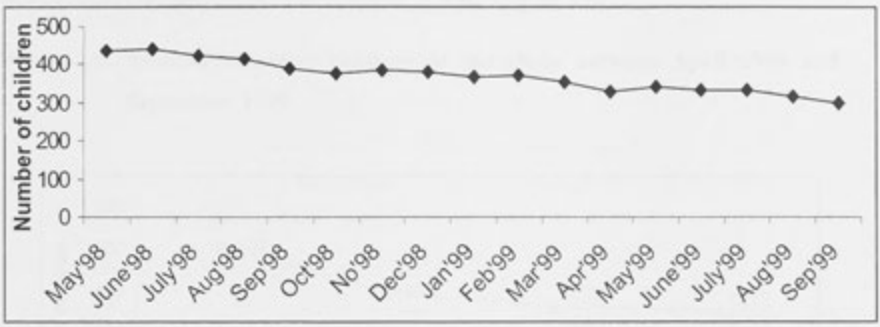
Table 4.4: Characteristics of parents and family (n=477)

Characteristics (number of respondents)	Number
Age of father (462)	Mean 33 years
	(range 18-52 years)
Age of mother (465)	Mean 31 years
	(range 16-44 years)
Education of father (456)	
High school	138 (30)
Trades or TAFE	148 (33)
University graduate	106 (23)
Postgraduate	64 (14)
Education of mother (466)	
High school	163 (35)
Trades or TAFE	144 (31)
University graduate	115 (25)
Postgraduate	44 (9)
Family income (446)	
<30,000	86 (19)
31,000-45,000	93 (21)
46,000-60,000	109 (24)
>60,000	158 (35)
Smoking by a family member (458)	
No smoking	315 (69)
Smoke	143 (31)
Duration of pregnancy for the child (469)	
36 weeks or less	31 (7)
>36 weeks	438 (93)
Type of delivery of the child (469)	
Normal vaginal delivery	325 (69)
Other than normal vaginal delivery	144 (31)

4.6. Loss to follow-up

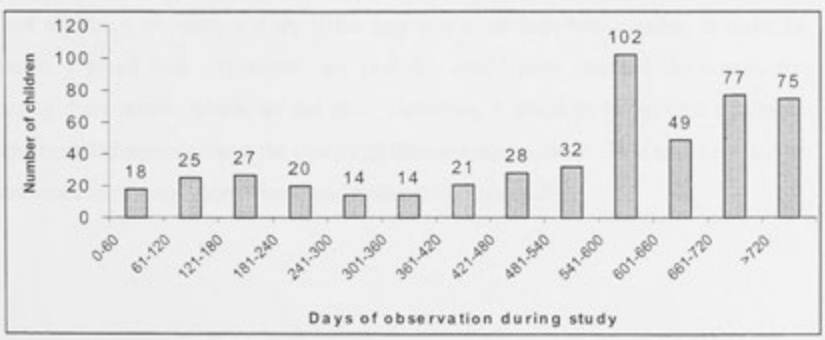
At the end of recruitment in April 1998, a total of 502 children were active in the study. Of the 502 children, 71% (355/502) remained active at the end of the study in September 1999. The involvement of the children in the study was mainly determined from the monthly diary return by the parents; the number of diary returns was variable throughout the period (Figure 4.4).

Figure 4.4: Diary return by the parents between May 1998 and September 1999



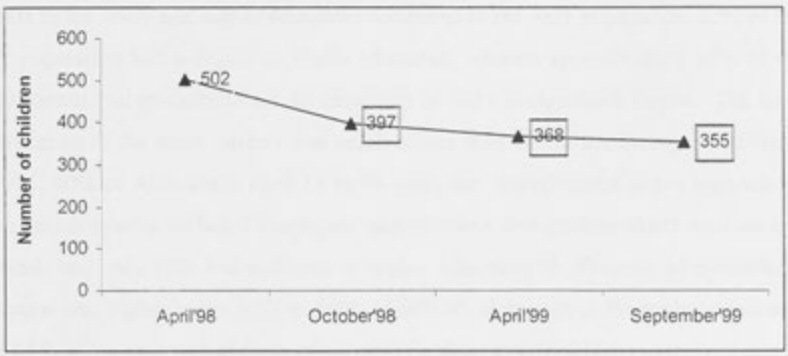
The period of observation for the children was based on the number of daily diaries returned by the parents. There was a total of 251,051 observation days from 502 children during the 25 months with a mean of 501 days. The period of diary observation varied between children, ranging from 28 days to 760 days. A total of 303 children were observed for more than 70% (540/760) of the total study period (Figure 4.5).

Figure 4.5: Days of observation for 502 children within the 760 days of study



A total of 147 children left the cohort at some time between May 1998 and September 1999; we failed to determine the exact time when these children actually dropped out from the study. In spite of all the efforts to maintain a good participation rate, diaries were not returned every month; this was a particular problem when we lost contact with parents as they moved to a new place without informing us or their GPs of a new address. However, we removed a child from the study if we did not receive a diary for the child for six consecutive months. The major dropout of children was observed six months after the completion of recruitment in April (Figure 4.6).

Figure 4.6: Number of active children in the study between April 1998 and September 1999



Interestingly, a few parents started sending a diary after a prolonged silence and apologised for misplacing diaries, mostly during the difficulties of moving house. We did not ask them to return a diary if the gap was more than two months, in order to minimise a recall bias. However, we probably could have checked the reason for restarting diary return, which we did not. Therefore, it could be an episode of illness which reminded parents about the study and thus to return a diary. This may have led to overestimation of respiratory illness and treatment in this study.

4.7. Generalisability

The study GPs were representative of Australian GPs regarding clinical practice. The majority of Australian GPs work in group practices, as in the study population.[157] The average hours of work in the surgery per week were a little shorter for the study GPs compared to the average Australian GPs (40 hours versus 43 hours).[158] However, this difference was probably due to there being more female GPs in the study than the national average (42% versus 31%), because female GPs work shorter surgery hours than their male counterparts.

The demographic details of the study children and their parents were compared to the 1996 Census of Population and Housing by the Australian Bureau of Statistics (ABS). There were more girls in the study compared to the national average and ACT average: 54.5% of the study children compared to 49% of the ACT population were females. Parents in the study had higher education compared to the ACT population: 27% of the ACT population had a degree or higher education, whereas approximately 35% of the study parents had graduated from an university or had a postgraduate degree. The level of education of the study parents was much higher than that of the average Australian. In 1996, 40% of Australians aged 15 to 64 years had qualifications above high-school level, which mainly included vocational qualifications and undergraduate or associate diploma, and only 14% had a degree or higher education.[159] The rate of post-school education was higher in the ACT in 1996, at 50%.[159] However, in the study population, over 65% of the parents had post-school qualifications and 35% had a university degree or a postgraduate degree. The family income of the study population compared well with the average family income of the ACT. The median gross income of couples with dependent children in the ACT was AS57,000 per annum in 1996, which was higher than the national average income.[159]

4.8. Discussion

The final sample of children in the study was smaller than had been intended and the recruitment process took much longer than had been anticipated. The reality of general practice is that it not only serves sick people, but is now also an important area for clinical research. During the recruitment stage of this study, several GPs indicated that they were already participating in other research trials. The slow recruitment of children may have been partly due to the pressure of GP commitments. We anticipated this problem in the design phase and aimed to involve the receptionist as the first point of child recruitment. It was proposed that the receptionist would attach a recruitment form with the case file of each successive child aged under two years, until 15 children from the practice were recruited. We hoped that this would reduce the work of recruitment for the GP, as well as being a reminder to the GP. However, most of the GPs decided to keep all the responsibilities themselves to reduce the pressure on the receptionists. As a result, we found that GPs apparently did not approach every successive child under two years of age who came to their practices. Sometimes, they selected patients from their practice lists. These facts lead obviously to some selection biases in the recruitment of patients, as seen from the social and educational profile of the parents.

A consequence of the longer child recruitment period that is particularly detrimental to the issues explored in this thesis was that we had a short data-collection phase before the first round of nasal swabs, in March-April 1998. The resulting small number of diaries reduced the power of the study to detect a significant association between antibiotic use before swab collection and antibiotic-resistance. However, despite the small number of diaries before the first swab, definitive results were obtained (Chapter 6).

Chapter 5 Surveillance of respiratory illness, antibiotic use and antibiotic-resistance

5.1. Overview

This chapter reports the descriptive analysis of respiratory illness and treatment in children during the study period. It also presents the pneumococcal carriage and pneumococcal resistance to antibiotics in the cohort over the time period. Respiratory illness was monitored by a daily diary recorded by the parents. Parents also recorded the detailed management of illness which included antibiotic use by the children. Pneumococcal carriage was monitored by a nasal swab collection from the children four times during the study. Pneumococcal isolates were tested for their sensitivity to six commonly used antibiotics to determine antibiotic-resistance.

5.2. Respiratory illness and management

5.2.1. Methods

Surveillance of respiratory illness was carried out for a total of 760 days (25 months) extending from September 1997 to September 1999. Parents maintained a respiratory health record for their children by completing a daily diary during the 25 months. The diary allowed parents to record the presence of 12 respiratory symptoms and signs: runny nose, blocked nose, green nasal discharge, dry cough, moist cough, wheeze, hoarse voice, sore throat, earache and ear discharge, cold and fever. 'Cold' was used by the parents as a summary description of respiratory illness rather than one specific symptom.[160] We therefore decided to keep 'cold' as a separate item for parents to report. In the daily diary, parents also reported the detailed management of respiratory illnesses in children including any doctor or hospital visit with the reason for the visit and treatment and duration of treatment of the children.

5.2.2. Respiratory illness

At the end of recruitment we had a sample of 502 children whose parents had agreed to participate in the study (Chapter 4). There was a total of 251,051 observation days from 502 children during the 25 months.

Respiratory symptoms

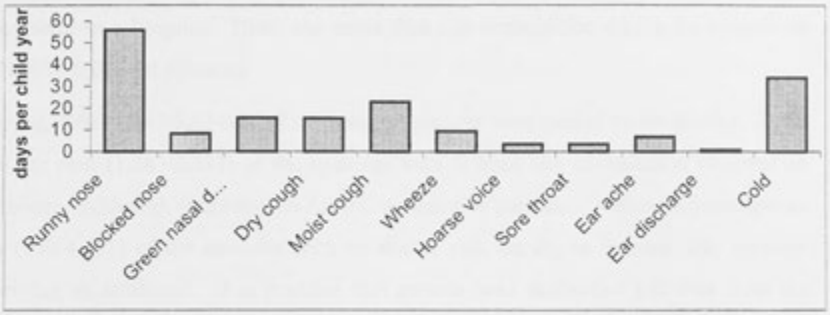
Days of a symptom per child-year were computed for each child by dividing the total number of days on which that symptom was observed by the total days for which diary records were available. For the whole population of children a mean was obtained from the estimates for individual children. The most common symptom experienced by the children was runny nose (Table 5.1).

Table 5.1: Days of respiratory symptoms for 502 children observed for 251,051 days between September 1997 and September 1999

Respiratory symptoms	Total number of days with symptom	Days per child-year
Runny nose	38257	54.2
Blocked nose	5941	8.1
Green nasal discharge	10572	15.2
Dry cough	10702	14.8
Moist cough	15562	22.3
Wheeze	5681	9.0
Hoarse voice	2182	3.3
Sore throat	2320	3.3
Earache	4332	6.7
Ear discharge	265	0.6
Fever	5567	8.0
Cold	23373	33.2

Runny nose accounted for 15% of the total observation days for children with a rate of 54 days per child-year. Children also had a high incidence of 'cold', at a rate of 33 days per child-year.

Figure 5.1: Number of days of symptoms per child-year



Respiratory episodes

A respiratory episode was defined as the presence of any of the above mentioned symptoms for at least two consecutive days, and an episode ended when there were two symptom-free days. Children recorded a total of 6,824 respiratory episodes during the 25 months with a rate of 9.9 episodes per child-year. Episodes per child-year were computed in the same way the symptom rate per child-year was computed. Children most commonly suffered from upper respiratory episodes which constituted 45% of all respiratory episodes (Table 5.2).

Table 5.2: Incidence of different types of episodes in 502 children observed for 251,051 days

Episode	Number	Episodes/child-year
Total respiratory episodes	6824	9.9
Upper respiratory episode	3062	4.4
Lower respiratory episode	1554	2.2
Throat episodes	856	1.2
Ear episode	1127	1.7
Fever only episodes	225	0.4

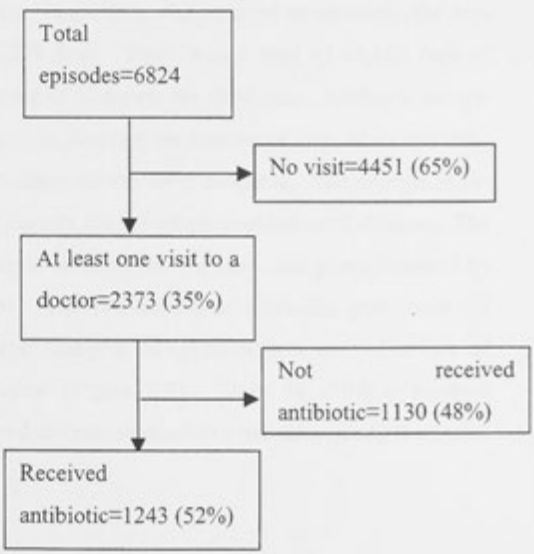
5.2.3. Management of respiratory illness

Of the 6,824 respiratory episodes, 35% (2,373/6,824) of episodes had at least one visit to a doctor or a hospital. There was more than one consultation during the episode in 10% (680/6,824) of episodes.

Overall, 20% (1,383/6,824) of all respiratory episodes were treated by antibiotics. Fifty-two per cent (1,243/2,373) of the episodes with at least one consultation received an antibiotic. Although antibiotics in Australia cannot be purchased without a prescription, 3% (140/4,451) of the episodes with no doctor visit during an episode also reported receiving an antibiotic. It is possible that parents used antibiotics left over from the previous prescription, or a doctor visit was not mentioned in the diary by parents.

Highest antibiotic use was recorded for ear episodes: 51% (572/1127) of all ear episodes were treated with antibiotics compared to 31% (264/856) of throat episodes and 19% (297/1554) of lower respiratory episodes. Seven per cent (221/3,062) of upper respiratory episodes also received antibiotics. The episodes that consisted of only fever were mostly diagnosed and treated as ear infections with 13% (29/225) receiving antibiotics.

Figure 5.2: Overview of respiratory episodes experienced by the children between September 1997 and September 1999



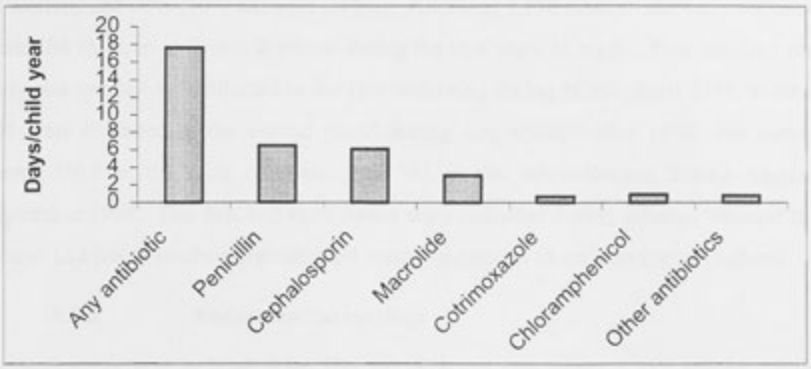
5.2.4. Total antibiotic use by the children

Children in the study commonly received one of three types of antibiotics: penicillin, cephalosporin or a macrolide. Commonly used penicillins in children were phenoxymethylpenicillin (Abbocillin) and amoxycillin (Amoxil, Alphamox, Cilamox); however some children also received a broader-spectrum penicillin like amoxycillin with potassium clavulanate (Augmentin). In this thesis, the term 'penicillin group' is used to refer to the entire group of penicillin used by the children. Commonly used cephalosporins in children were cephalexin (Keflex, Ibilex) and cefaclor (Ceclor). Cephalosporins as a group have a broader-spectrum of antibacterial activity than the penicillin group of antibiotics. Children also received cotrimoxazole, which was mostly used for prevention of urinary tract infection. Chloramphenicol was also used in children as a topical anti-infective preparation for eye or ear. Among the other antibiotics used in children, metronidazole (Flagyl) was the commonest.

There were six children in the study who received antibiotics for more than half of their observation period. These six children received antibiotics for an average 237 days/child-year compared to 17.6 days/child-year for other children. I considered these six children different from average children regarding total antibiotic use and therefore, excluded them from the following analysis.

Of the remaining 496 children, 114 (23%) did not receive an antibiotic during the period for which their parents provided diaries. In children who received an antibiotic, the days of antibiotic use ranged from 1 to 221 days. There was a total of 12,309 days of antibiotic use for the children with a rate of 17.6 days per child-year. Antibiotic use per child-year was computed for each child by dividing the number of days when antibiotic was used by the total days for which diary records were available. The average of the estimates of all children determined the rate for the whole population of children. The most commonly used antibiotic group in children was the penicillin group followed by cephalosporin and macrolide groups. The rate of use of penicillin group was 6.5 days/child-year compared to 6.1 days/child-year of cephalosporin use. The rate of macrolide use was 3.1 days/child-year (Figure 5.3). Only 44 children received cotrimoxazole and 85 children received chloramphenicol at some time during the period of their observation.

Figure 5.3: Rate of antibiotic use (days per child-year) in 496 children



5.3. Pneumococcal carriage and antibiotic-resistance

5.3.1. Methods

To monitor the pneumococcal carriage and antibiotic-resistance level in the study children, we collected a nasal swab from each study child four times during the two years of study. I described the detailed protocol of swab collection and laboratory procedure for culture of pneumococci in Chapter 3. Pneumococcal isolates collected from the children were tested for susceptibility to penicillin, erythromycin, cotrimoxazole, tetracycline, cholramphenicol and cefotaxime by disc diffusion tests. The minimum inhibitory concentrations (MIC) of penicillin, erythromycin and cefotaxime were also determined by the E-test. The interpretive criteria of the NCCLS[161] were used for susceptibility categorisation of E-test values. Antibiotic-resistance was defined as decreased susceptibility to antibiotics, which included both intermediate and high-level resistance. Multi-drug resistance was defined as decreased susceptibility to two or more antibiotics.

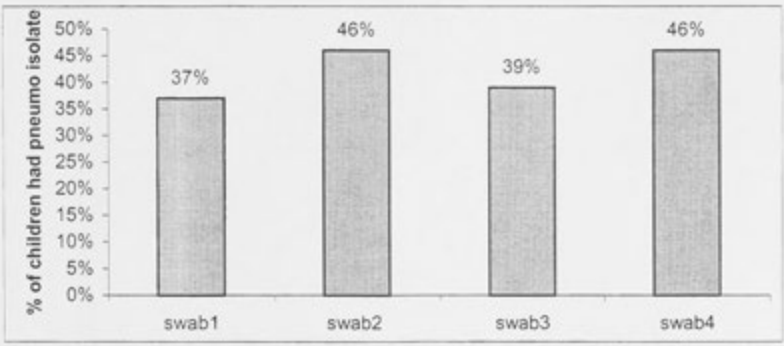
5.3.2. Nasal swab collection

Of the 502 study children, 96% (484) attended at least one of the four nasal swab collections and 60% (303) attended all four. A total of 1,576 nasal swabs were collected from 484 children in four collections during the two years of study. Four hundred and sixty-one swabs were collected in the first collection during March-April 1998, another 405 were collected in the second round during August-September 1998, 369 during March 1999 in the third collection and 341 in the last collection during August-September 1999. The first and third swabs were collected during autumn, whereas the second and fourth swabs were collected during late winter to early spring in Canberra.

5.3.3. Pneumococcal carriage

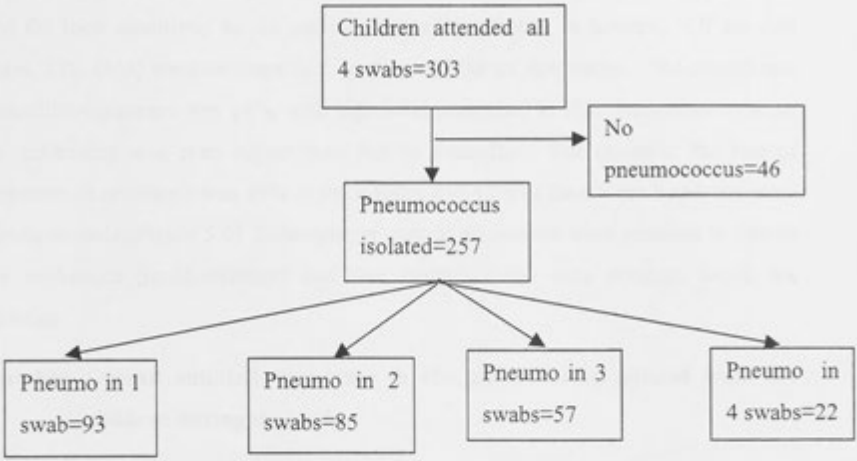
Pneumococcus was isolated from 654 of 1576 (41.5%) swabs. The pneumococcal carriage rate was higher during the winter collections compared to those collected in autumn.

Figure 5.4: Pneumococcal carriage rate in 484 children in four swabs



Of the 303 children who attended all four swab collections, a pneumococcus was isolated at least once from 85% (257) of them. Among these 257 children, 48% (124) carried pneumococci on two or more successive collections and 9% (22) carried a pneumococcus on all four occasions. However, as we did not test for serotyping of the isolates, it is not possible to decide if the children had a prolonged carriage of the same strain or if they acquired new strains.

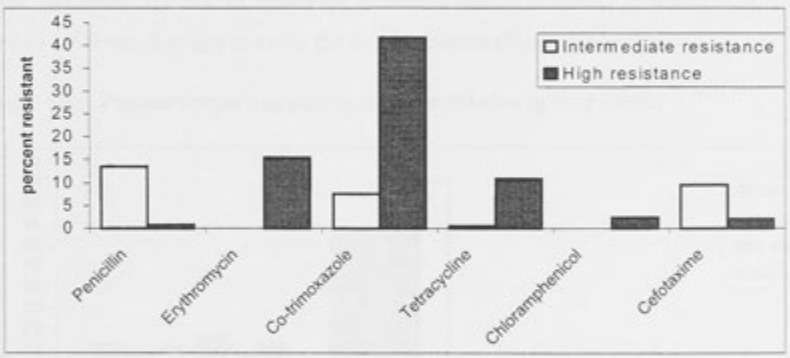
Figure 5.5: Pneumococcal carriage in children who attended all four swab collections



5.3.4. Antibiotic-resistance in pneumococci

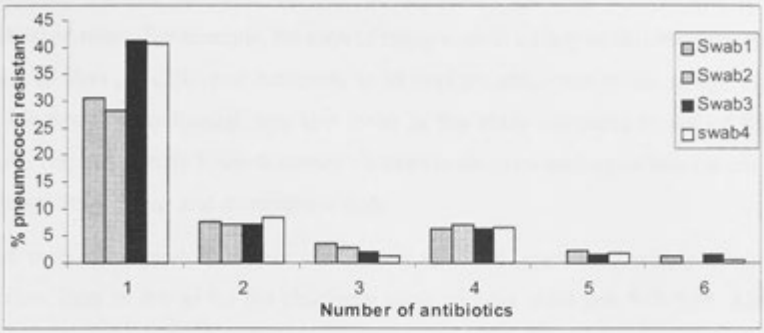
A total of 654 pneumococcal positive swabs were collected from 484 children and were tested for their sensitivity to six commonly used antibiotics in humans. Of the 654 isolates, 53% (348) were resistant to at least one of the six antibiotics. The overall rate of penicillin-resistance was 14%, with high-level resistance in 1%. Resistance to some other antibiotics was even higher than that to penicillin. For example, the rate of cotrimoxazole resistance was 49% in the isolates and 42% of them were highly resistant to cotrimoxazole.(Figure 5.6) Nineteen per cent of all isolates were resistant to two or more antibiotics (multi-resistant) and five isolates (1%) were resistant to all six antibiotics.

Figure 5.6: Overall antibiotic-resistance in 654 pneumococci, isolated from 484 children during the study



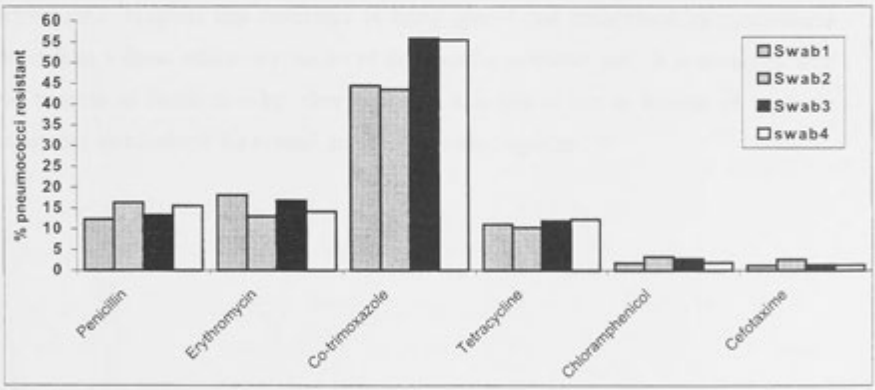
Nasal swabs were collected twice in 1998 and twice in 1999. The percentage of pneumococcal isolates that were sensitive to all of the six antibiotics decreased from about 50% in 1998 to 40% in 1999. Conversely, the percentage of pneumococci resistant to at least one antibiotic increased from approximately 30% in 1998 to 40% in 1999 (Figure 5.7).

Figure 5.7: Pneumococcal isolates resistant to the number of antibiotics in four swabs



The rate of resistance to most of the antibiotics did not change significantly over the two years. However, the rate of resistance to cotrimoxazole increased by about 10% from 1998 to 1999 which might increase the total resistance.(Figure 5.8)

Figure 5.8: Pneumococcal resistance to six antibiotics in four swabs



5.4. Discussion

Children in the study, in general, had fewer days of symptoms than those in other published studies, although the rate of respiratory episodes was similar to other published rates. For example, the days of runny nose in a study of children by Roberts[154] were 89 days per child-year compared to 56 days per child-year in this study. The rate of blocked nose and cough was also lower in this study compared to that of Roberts. However, in her study Roberts studied children in day-care settings, where the incidence of respiratory illness and morbidity is high.

The rates of respiratory illness in children aged 0-5 years vary widely in different studies, from as low as 6.1 per child-year up to 15.7 per child-year.[33,153,162-164] Although we used more symptoms to define a respiratory illness in this study, the incidence of 9.9 per child-year is still comparable with other studies.

The increase in the rate of pneumococcal resistance to antibiotics has been reported in Australia and around the world.[4,165] In the present study, resistance to one antibiotic increased by 10% within only one year from 1998 to 1999.

Resistance to the antibiotics that are not commonly prescribed for children, e.g. tetracycline, suggests that resistance is being spread and maintained by mechanisms other than a direct selective pressure of the specific antibiotic use. It is consisted with the process of coselection by other antibiotic use, that is due to sharing of the same resistance mechanisms for several drugs in the same organism.[122]

Chapter 6 Penicillin-resistance in pneumococci

6.1. Overview

This chapter presents the results of the effect of antibiotic use on antibiotic-resistance in pneumococci. Children in this study commonly received beta lactam antibiotics (penicillin, cephalosporin). Pneumococcal resistance to all beta lactam antibiotics is believed to be entirely due to the development of altered penicillin-binding proteins (PBPs),[105] so that resistance to one beta lactam antibiotic tends to follow resistance to the other. In this chapter, I explored the association between the use of beta lactam antibiotics in children and the isolation of penicillin-resistant pneumococci. I performed two steps in the analysis.

First, I explored if there was any association between use of any beta lactam antibiotic during periods preceding isolation of a penicillin-resistant pneumococcus. Antibiotic use in children could be monitored for a maximum of 24 months before a swab collection. This 24-months period was split into 12 two-month periods to explore the temporal association of beta lactam use with penicillin-resistance. I separately explored the relationship of penicillin group use, cephalosporin use and combined use of penicillin group and cephalosporin with penicillin-resistance during those periods.

Second, I explored if duration of use of beta lactam antibiotic in children was related to the likelihood of a pneumococcus to be resistant to penicillin. For this analysis, I used total beta lactam antibiotic use in children during the six months before collecting a positive pneumococcal swab. This association was also explored for use of penicillin group and cephalosporin separately during that period.

I also paid particular attention to the antibiotic-resistance profile of the pneumococcal isolates collected from the children who received long-term antibiotics during the study.

6.2. Methods

To detect the effect of use of beta lactam antibiotics on penicillin-resistance, I included the data collected throughout the study period extending from September 1997 to September 1999. Information regarding children's health and treatment was determined from the daily diary recorded by the parents. Pneumococcal resistance to penicillin was monitored by testing nasal swabs from the study children four times during the two years. The procedure of nasal swab collection is detailed in Appendix 3. Pneumococcal isolates were identified by colonial morphology, α-haemolysis on blood agar plates, susceptibility to optochin and/or bile solubility. Only the most predominant colony of each pneumococcal isolate was tested for susceptibility to penicillin, erythromycin, cotrimoxazole, tetracycline, chloramphenicol and cefotaxime. The isolates were defined as sensitive to penicillin when minimal inhibitory concentration (MIC) was less than or equal to 0.064 mg/L, intermediate-resistant when MIC was greater than 0.064 mg/L but less than or equal to 1 mg/L, and highly resistant when MIC was greater than 1 mg/L. The detailed laboratory procedures for isolation of pneumococcus and sensitivity test to antibiotics are described in Chapter 3.

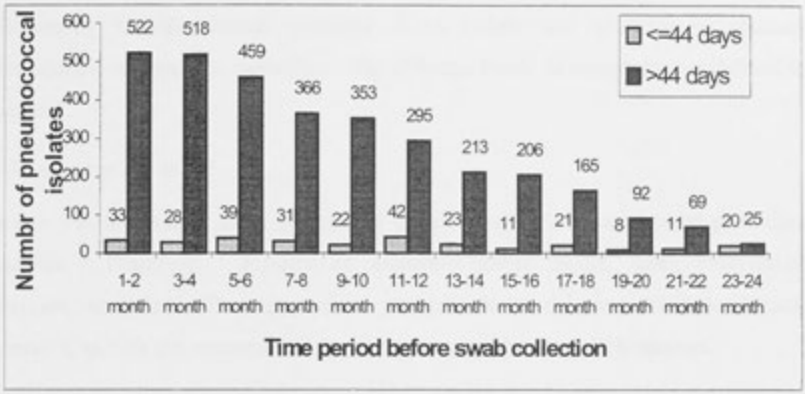
6.2.1. Inclusion criteria

A total of 654 swabs positive for pneumococcus were isolated from 484 children in four collections. I excluded 17 of the 654 pneumococcal isolates collected from the children for whom we did not receive any diary. Another six pneumococcal positive swabs were collected from the children who received prophylactic antibiotics during the study. I defined prophylaxis as antibiotic use for more than half of the observation period before collection of a nasal swab. Children who were on prophylaxis received antibiotics for an average of 237 days/child-year compared to 18 days/child-year for other children. I considered the isolates collected from these children as a separate entity regarding their resistance status. Therefore, the main analysis was performed with 631 pneumococcal isolates (654-23=631). However, the six isolates were analysed separately.

6.2.2. Period of observation before swab collection

Children had a maximum of six months of observation before the first swab, 12 months before the second swab, 18 months before the third swab and 24 months before the fourth swab collection. The time period before the date of each swab collection was split into 12 two-month periods. I wanted to determine if there was any specific period before the isolation of pneumococcus during which beta lactam antibiotic use was particularly likely to be associated with penicillin-resistance. Because not all children returned all diaries, we had variable information for each of the 60 day periods. The available diary observation for children ranged from a minimum of 27 days to a maximum of 60 days within each two-monthly period. In Figure 6.1 I have grouped the pneumococcal isolates into those for which less than 75% of days were documented (27-44 days) and those for which 75% or more of days (>=44 days) were documented. Eighty-eight per cent (555/631) of the isolates were collected from the children who had some observation during the first two months before swab collection. Among the 555 isolates, 94% (522/555) were isolated from children who were observed for at least 75% of the first 60 days before the swab. The number of isolates for which observation was available gradually reduced as I sought to discover the effects of beta lactam use at up to two years before the isolation. A few children had more than 18 months of observation before a swab. For example, 16% (100/631) of the isolates were collected from the children who had some observation during 19-20 months before swab collection and 92 of these isolates had information about antibiotic use for more than 44 days (Figure 6.1). To limit the likelihood of misclassification of exposure to antibiotics, I excluded from the analysis pneumococcal isolates that were collected from children who were observed for less than 75% of the 60 days (<44 days) during the two monthly time period. Thus for the 19-20 month period my analysis was based on the 92 isolates for which 75% or more of days were observed in that period.

Figure 6.1: Days of observation within each two months associated with positive pneumococcal swabs



6.3. Association of beta lactam antibiotic use with isolation of penicillin-resistant pneumococci

Of the total 631 eligible pneumococcal isolates, 14% (86/631) were resistant to penicillin. Beta lactam antibiotic use during a period implied either use of penicillin group or use of cephalosporin or both penicillin group and cephalosporin use during that period. In this section, first, I assessed if there was an association between any beta lactam use during a period and the rate of isolation of penicillin-resistant pneumococci. Then the risk was assessed separately for penicillin group use, cephalosporin use and use of both penicillin group and cephalosporin during a period.

6.3.1. Effect of any beta lactam antibiotic use with isolation of penicillin-resistant pneumococci

Exposure variable

The exposure variable was use of a beta lactam antibiotic during a particular period (beta). The variable was a dichotomous variable, which indicated any beta lactam use versus no beta lactam use during a period.

Outcome variable

The outcome variable was pneumococcal resistance to penicillin (pen); resistance included either intermediate or high resistance to penicillin. The variable was a dichotomous variable, which indicated if an isolate was sensitive or resistant (intermediate or highly) to penicillin. The different levels of sensitivity are defined in Chapter 3.

Selection of the model

My aim was to obtain a valid estimate of the effect of beta lactam use on penicillin-resistance. Therefore, I selected an exposure-disease model, using multivariate regression analysis. The appropriate multivariate model was multiple logistic regression, as both the outcome and the exposure variables were dichotomous.

Adjustment for clustering

A pneumococcal isolate was collected from a child as many as four times during the four collections over the two years. The pneumococcal isolates of a child are not necessarily independent, regarding their resistance status. Therefore, the isolates from the same child cannot be regarded as independent for the purpose of analysis. Thus I performed both univariate and multivariate analysis by using logistic regression in STATA, that allowed adjustment for the impact of clustering within a child. I estimated robust standard error, which relaxes the assumption of independence of the observations for correlated observations within a child.

The command I used in STATA for univariate analysis to detect the effect of use of any beta lactam antibiotics on penicillin-resistance was:

Logistic pen beta, cl(idno)

where

pen=resistance to penicillin (yes/no)

beta=use of beta lactam antibiotics during the period(yes/no)

cl(idno)=clustered by child identification number.

Univariate analysis

The risk of penicillin-resistance was compared for each period between the isolates collected from the children who received beta lactam antibiotics and those collected from the children who did not receive any. Beta lactam use was grouped as either use of beta lactam antibiotic at least for a day, or no beta lactam use at all during the period. Penicillin-resistance was also a dichotomous variable, and grouped as either sensitive or resistant to penicillin. Of the total 631 pneumococcal isolates, 86 (14%) were resistant to penicillin. The number of isolates would be different in different time periods depending on the corresponding number of days of observation in that period. The use of beta lactam antibiotics during each two monthly period was tested for its association with penicillin-resistance. However, a child might receive beta lactam antibiotics in more than one period of time. If there was a significant association observed between penicillin-resistance and beta lactam use in a period, I examined if the association was affected by the use of beta lactam in an earlier period. The risk of having a penicillin-resistant pneumococcal isolate was 1.8 times higher in those who used beta lactam antibiotics during the immediate two months period before the swab was collected (RR 1.8, p=0.01) (Table 6.1). A significant risk was also observed for the beta lactam use during the 19-20 months before swab collection (RR 2.9, p=0.02) (Table 6.1).

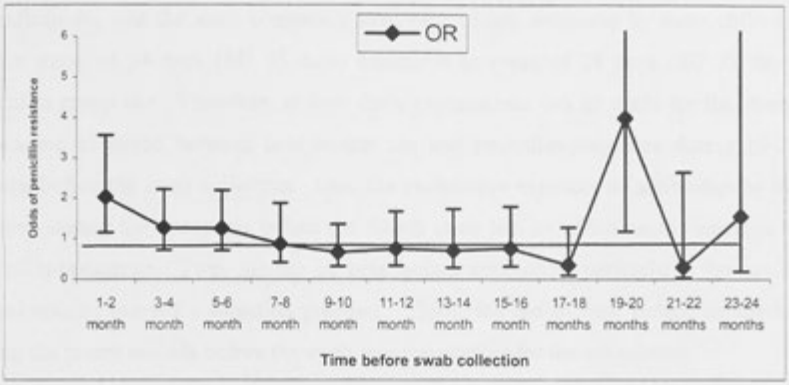
Table 6.1: Crude relative risk of penicillin-resistance among the exposed compared to those non-exposed by 2-months period

Time before swab collection	Penicillin-resistant isolates/total isolates with beta lactam	Penicillin-resistant isolates/total isolates with no beta lactam	RR	p (2 sided Fisher's exact)
0-2 months	22/98	53/424	1.8	0.01
3-4 months	18/111	54/407	1.2	0.43
5-6 months	19/110	50/349	1.2	0.45
7-8 months	10/73	45/293	0.9	0.72
9-10 months	11/100	40/253	0.7	0.25
11-12 months	9/78	32/217	0.8	0.48
13-14 months	7/62	23/151	0.7	0.45
15-16 months	8/63	23/143	0.8	0.53
17-18 months	3/40	23/125	0.4	0.10
19-20 months	6/17	9/75	2.9	0.02
21-22 months	1/14	11/55	0.4	0.26
23-24 months	2/8	3/17	1.4	0.67

I measured the effect of beta lactam use on penicillin-resistance in a logistic regression model adjusting for the cluster effect of repeated positive swabs in a child (Appendix 6.1). The adjusted results were qualitatively similar to the crude effect that is shown in table 6.1. In the adjusted model, the odds of penicillin-resistance was double for those who used beta lactam during the previous 2 months (OR 2.03, 95% CI 1.15-3.56, p=0.01). The adjusted odds of penicillin-resistance for beta lactam use during the 19-20 months was also significantly high, but because of the small number of exposed isolates in this period the association had an wide confidence interval (OR 4.00, 95% CI 1.18-13.56, p=0.03) (Appendix 6.1).

The risk of penicillin-resistance gradually decreased as the duration from time of beta lactam use to the date of swab collection became longer (Figure 6.2).

Figure 6.2: Odds ratio of penicillin-resistance for children with any beta lactam use at different periods before swab collection, adjusted for repeated pneumococci from the same child



The point estimate of having penicillin-resistant pneumococcal isolate was greater than 1 for the children who used beta lactam antibiotics during the 0-6 months before swab collection (Figure 6.2). However, the association between beta lactam use and isolation of penicillin-resistant isolate was only significant for the period of 0-2 months before swab collection. The point estimate was also high for the association during 19-20 months, but with a wide confidence interval.

Because of the consistency of the finding for the particular period of 19-20 months, the association was further explored. A total of six penicillin-resistant isolates were collected from children who had received beta lactam antibiotics 19-20 months before the swabs. They were collected from six different children and a penicillin-resistant pneumococcus was isolated from all of them during the fourth swab. All six isolates were resistant to penicillin and cotrimoxazole, and five of them were also resistant to erythromycin and tetracycline; only one isolate was resistant to chloramphenicol. All six children had also received a beta lactam antibiotic during more recent periods and three of them received it during the six months before the swab collection. Although these children were not included in the group of children with prophylaxis by definition, they were high antibiotic users compared to other children. For example, these six children had a mean of 77 days (SD 60 days) of antibiotic use during the study

compared to a mean of 18 days (SD 24 days) for all children from whom a pneumococcal isolate was collected, except those with prophylactic antibiotic use. The most commonly used antibiotic in these six children was beta lactam antibiotic with a mean of 52 days (SD 48 days) and macrolide with a mean of 25 days (SD 25 days). Cephalosporin was the most commonly used beta lactam antibiotic by these children, with a mean of 34 days (SD 33 days) compared to mean of 18 days (SD 25 days) penicillin group use. Therefore, at least three explanations can be made for the strong association observed between beta lactam use and penicillin-resistance during 19-20 months before the swab collection. One, the cumulative exposure of antibiotics by the children during the two years before the fourth swab had an effect on the carriage of penicillin-resistance. Two, the use of beta lactam antibiotics, particularly the use of cephalosporin, exerted a selection pressure. Third, the use of beta lactam antibiotics during the recent periods before the swab was responsible for the association.

Multivariate analysis

I set out to obtain an overall estimate of the effect of beta lactam use during the two months before swab collection on penicillin-resistance, after adjusting for a range of confounding factors. I followed the stages of developing a multivariate model suggested by Kleinbaum.[156] I started modelling with specification of the variables, followed by interaction assessment, and completed with assessment of confounding.

Variable specification

I selected potentially confounding variables that could be biologically associated with penicillin-resistance or that had been shown in previous studies to be related to penicillin-resistance. These included demographic and environmental variables, and variables related to health and treatment of children (Tables 6.2-6.4).

Age was included because several studies reported that younger children are more likely to carry a resistant strain of pneumococcus than older children.[8,129] Gender was included because Melander et al. found that the carriers of penicillin-resistant pneumococci were more often of male sex than the non-carriers.[129] However, another study found no association between sex of the child and carriage of resistant pneumococci.[8]

Day-care attendance is frequently reported as an important factor to influence the epidemiology of resistant bacteria. Henderson found that a higher proportion of

pneumococci recovered from children in a day-care centre were resistant to beta lactam antibiotics and also to trimethoprim-sulphamethoxazole, compared to the organisms isolated from patients at a tertiary care hospital.[114]

A visit to a doctor or hospital was considered as a potential confounding variable because of the likelihood of a child being exposed to other patients in the waiting room, which may increase the chance of acquiring a resistant bacteria. The more often a child visited a doctor, the more likely that she/he would receive an antibiotic. However, if a child did not visit a doctor or hospital at all, she/he is not likely to take an antibiotic. Therefore, this variable was not included in the model.

Type of respiratory episode was also considered as a potential confounder. However, the type of episode is unlikely to be related to antibiotic-resistance independently of its association with antibiotic use. The antibiotic use in an episode depends on the type of episode. For example, if a child had an ear episode she/he was more likely to receive antibiotics than another child who had no ear episode. Therefore, this variable was also excluded as it was also not used in the model.

Table 6.2: Demographic characteristics of children

Variable description	Form of the variable
Age of child at the time of swab collection	Continuous
Sex of child	Dichotomous M=0, F=1

Table 6.3: Environmental variables

Variable description	Form of variable
Type of day-care attended by the child at the time of swab collection	Categorical 1=single care by parent or by nanny 2=small group care (2-6 children/care) 3=large group care (>6 children/care)
Duration of day-care	Categorical 0=no day-care 1=1-20 hr/wk 2=21-40 hr/wk 3=>40 hr/wk
Number of siblings	Categorical 0=no sibling 1=1 sibling 2=2-5 siblings
Presence of older siblings	Dichotomous 0=no older sibling 1=1 or more older siblings
Season of swab collection	Dichotomous 1=autumn 2=winter/early spring

Table 6.4: Health and treatment-related variables

Variable description	Form of variable
Any hospital admission during the period	Dichotomous 0=no, 1=yes

Assessment of interaction

All the variables except any hospital admission (Tables 6.2-6.4) were tested by using logistic regression to determine if there was evidence of effect modification. Hospital admission could not be tested for evidence of effect modification because of the very low number of admissions. Ten of the 522 isolates had a hospital admission, six of them had some beta lactam use and one of them was resistant to penicillin. I tested other variables for interactions with the beta lactam use during the two months using the Likelihood Ratio test. The test assessed the deviation between the model with the interaction term and the confounder, and the model with only confounder. None of the interaction terms was statistically significant by the Likelihood Ratio test (Table 6.5).

Table 6.5: Impact of interaction terms by using Likelihood Ratio test in logistic regression model

Interaction terms	P value in Likelihood Ratio test
Beta lactam use*age	0.55
Beta lactam use*sex	0.67
Beta lactam use*number of siblings	0.69
Beta lactam use*presence of older sibling	0.98
Beta lactam use*type of day-care	0.60
Beta lactam use*duration of day-care	0.89
Beta lactam use*season of swab collection	0.48

Assessment of confounding

I assessed confounding by using logistic regression. To determine if a variable was a confounder I first obtained a crude overall estimate of the association between exposure and outcome, adjusting for repeated positive swabs isolated from a child. Then I controlled the association for each variable at a time and observed if the addition of a variable altered the estimate of the association between the exposure and the outcome. A potential confounder would be considered a confounder if adjustment for the variable resulted in a meaningful change of the association between the exposure and the outcome.[166] A 10% or greater distortion of odds ratio from the crude was considered as

a meaningful distortion. The results of this confounding assessment are shown in Table 6.6.

Table 6.6: Evaluation of confounding for distortion of effect of any beta lactam use during two months immediately before swab collection on penicillin-resistance (n=522 isolates)

Variables	OR	Evaluation
Crude OR between penicillin-resistance and beta lactam use	2.03	
Adjusted for age	2.01	Not a confounder
Adjusted for sex	2.00	Not a confounder
Adjusted for number of siblings	2.00	Not a confounder
Adjusted for presence of older sibling	2.08	Not a confounder
Adjusted for type of day-care	2.11	Not a confounder
Adjusted for duration of day-care	2.08	Not a confounder
Adjusted for season of swab collection	1.98	Not a confounder
Adjusted for any hospital admission in two months	2.02	Not a confounder

None of the variables meaningfully distorted the relationship between penicillin-resistance and use of beta lactam antibiotic during the two months immediately before swab collection.

Final model

The final multivariate model was adjusted for the cluster effect of repeated pneumococcal positive swabs in the same child. Children who received beta lactam antibiotics during the two months immediately before the swab collection were twice as likely to carry a penicillin-resistant isolate as children who did not (OR 2.03, 95% CI 1.15-3.56, $p<0.01$) (Table 6.7).

Table 6.7: Final multivariate model between penicillin-resistance and any beta lactam use during the two months immediately before the swab collection, adjusted for cluster effect of child (n=522 pneumococcal isolates)

Variable	OR	Robust St error	Lower 95% CI	Upper 95% CI	P value
Beta lactam use in 2 months	2.03	0.58	1.15	3.56	0.01

I tested to see if beta lactam use during the 3-4 months had affected the finding of the relationship in the two months immediately before swabbing. Thirty-three pneumococcal positive swabs were collected from the children who received beta lactam antibiotics during the first two months, as well as during the 3-4 months. The association between beta lactam use during the two months immediately before swab collection and penicillin-resistance was still significant even after excluding the 33 isolates that had beta lactam use during both periods (OR 2.10, CI 1.09-4.06, p=0.03).

Of the 522 isolates that were included in the analysis of beta lactam use during the two months before the swab, 81% (424/522) were collected from children who did not receive any beta lactam and 19% (98/522) were from children who received a beta lactam antibiotic. Of the 98 isolates collected from the children who received a beta lactam, 38% (37/98 isolates) received penicillin group, 52% (51/98 isolates) received cephalosporin, and 10% (10/98 isolates) received both penicillin group and cephalosporin during that period. The risk of penicillin-resistance for each of these three groups of beta lactam use was examined separately to determine the effect of each particular pattern of beta lactam use on penicillin-resistance. The highest risk of penicillin-resistance was associated with the pneumococci isolated from the children who received both penicillin group and cephalosporin during that period and the association was statistically significant (Table 6.8). The risk of penicillin-resistance was 1.7 times higher in isolates collected from children who had only cephalosporin use and 1.5 times higher in the isolates from children who had only penicillin group use, than the isolates that did not have any beta lactam antibiotics during that period, however neither reached statistical significance (Table 6.8).

Table 6.8: Crude relative risk of penicillin-resistance in three groups of isolates with only penicillin group use, only cephalosporin use and both penicillin group and cephalosporin use during the two months before swab collection

Types of beta lactam use	Penicillin-resistant isolates/total isolates exposed	Penicillin-resistant isolates/total isolates not exposed	RR	P (2 sided Fisher's exact p)
Only penicillin group	7/37	53/424	1.5	0.27
Only cephalosporin	11/51	53/424	1.7	0.07
Both penicillin group and cephalosporin	4/10	53/424	3.2	0.01

After adjusting for the cluster effect of repeated positive swabs from the same child, the association of penicillin-resistance was still significant for the isolates collected from the children who received both penicillin group and cephalosporin during the two months period (OR 4.67, 95% CI 1.27-17.09, p=.02) (Appendix 6.2). Although the odds ratio was almost 5, the 95% confidence interval was wide because of small numbers of isolates from children who had been exposed to both antibiotics.

6.3.2. Effect of penicillin group use on the isolation of penicillin-resistant pneumococci

Univariate analysis

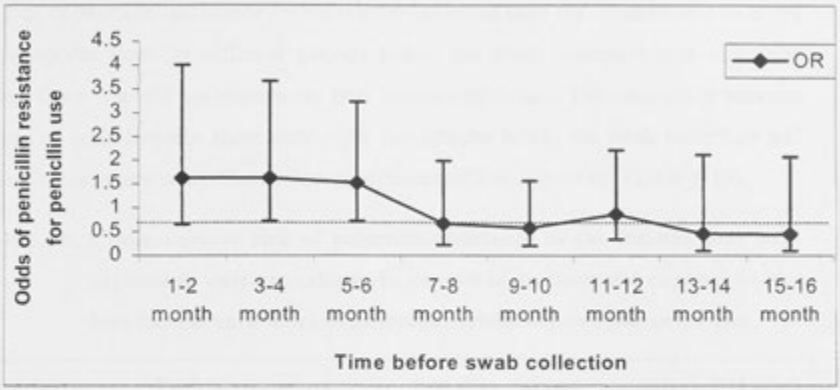
The risk of penicillin-resistance for the isolates collected from the children who received only penicillin group in different time periods before swab collection was compared to those who did not receive any beta lactam antibiotics. The risk of penicillin-resistance for the penicillin group use during the four months immediately before the swab was 1.5 times higher and for the use during 5-6 months was 1.4 times higher compared to no beta lactam use during those periods. None of the associations was statistically significant (Table 6.9).

Table 6.9: Crude relative risk of penicillin-resistance in the isolates that were exposed to only penicillin group compared to those not exposed to any beta lactam antibiotics in different periods before swab collection

Time before swab collection (months)	Penicillin-resistant isolates/total isolates with penicillin group only	Penicillin-resistant isolates/total isolates with no beta lactam	RR	P (2 sided Fisher's exact p)
0-2	7/37	53/424	1.5	0.27
3-4	8/40	54/407	1.5	0.24
5-6	10/49	50/349	1.4	0.27
7-8	4/37	45/293	0.7	0.46
9-10	5/51	40/253	0.6	0.27
11-12	6/46	32/217	0.9	0.77
13-14	2/26	23/151	0.5	0.31
15-16	2/25	23/143	0.5	0.29
17-18	0/20	23/125	0	
19-20	2/9	9/75	1.9	0.39
21-22	1/9	11/55	0.6	0.53
23-24	1/5	3/17	1.1	0.90

The association of penicillin group use during each two months with penicillin-resistance was adjusted for the repeated positive swabs collected from the same child. The adjusted risk of penicillin-resistance was about 1.5 times higher for the isolates collected from the children who had only penicillin group use during the 0-6 months before swab collection (Appendix 6.3). However, no association was statistically significant. The number of penicillin-resistant isolates from children who had received penicillin group was small in all periods. The smaller sample size might have reduced power to show a significant association. There was hardly any isolate in the resistant group after the 15-16 months period (Table 6.9). The direction of effect of penicillin group use on penicillin-resistance over time is suggestive of a dose response as shown in Figure 6.3.

Figure 6.3: Risk of penicillin-resistance for children with exclusive penicillin group use at different periods before swab collection, adjusted for repeated positive swabs from the same child



The point estimate of having a penicillin-resistant pneumococcus was greater than 1 for penicillin group use alone during the first six months before swab collection. A similar pattern of risk was also observed for any beta lactam use for the same period (Figure 6.2).

Multivariate analysis

I followed the same strategy to develop a multivariate model as I did for any beta lactam use during the two months before swab collection and penicillin-resistance. None of the variables (Tables 6.2-6.4) modified or confounded the effect of penicillin group use alone on penicillin-resistance. Therefore, the final model was adjusted only for repeated pneumococcal isolates collected from the same child. Children who received only penicillin group during the two months before collecting a swab were more likely to carry a penicillin-resistant isolate than the children who did not receive any beta lactam antibiotic; however, the association did not reach statistical significance (OR 1.63, 95% CI 0.66-4.01, p=0.29) (Appendix 6.3).

6.3.3. Effect of cephalosporin use alone on the isolation of penicillin-resistant pneumococci

Univariate analysis

The risk of penicillin-resistance for the isolates collected from the children who received cephalosporin alone in different periods before the swab collection was examined against those who did not receive any beta lactam antibiotics. The association between the use of cephalosporin alone during the two months before the swab collection and penicillin-resistance was of borderline significance (RR=1.7, p=0.07) (Table 6.10).

Table 6.10: Crude relative risk of penicillin-resistance in the isolates that were exposed to only cephalosporin compared to those not exposed to any beta lactam antibiotics in different periods before swab collection

Time before swab collection (months)	Penicillin-resistant isolates/total isolates with cephalosporin	Penicillin-resistant isolates/total isolates with no beta lactam	RR	P (2 sided Fisher's exact p)
0-2	11/51	53/424	1.7	0.07
3-4	7/58	54/407	0.9	0.80
5-6	7/53	50/349	0.9	0.83
7-8	6/29	45/293	1.3	0.45
9-10	2/36	40/253	0.4	0.10
11-12	1/24	32/217	0.3	0.15
13-14	3/29	23/151	0.7	0.49
15-16	5/29	23/143	1.1	0.88
17-18	1/16	23/125	0.3	0.22
19-20	4/7	9/75	4.8	0.002
21-22	0/5	11/55	0	
23-24	0/1	3/17	0	

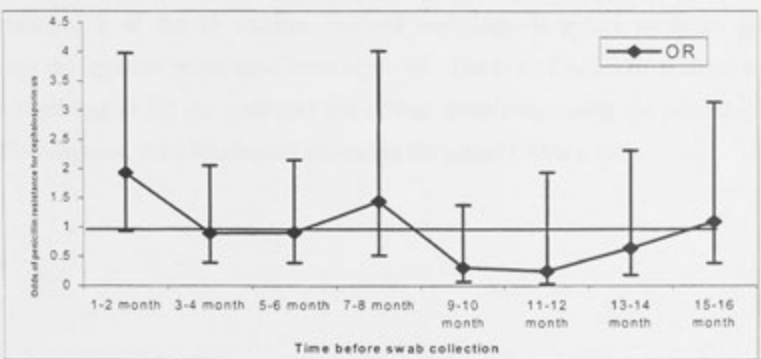
The association was also highly significant for cephalosporin use alone during the 19-20 months before the swab collection (Table 6.10). A similar association was also observed for any beta lactam use and penicillin-resistance during the same period (Table

6.1) and the isolates were also common in both analyses. The antibiotic use and the resistance pattern related to the exposed isolates during the 19-20 months before swab collection have been described previously.

The effect of cephalosporin use on penicillin-resistance was adjusted for cluster of repeated pneumococcal isolates collected from a child (Appendix 6.4). After adjusting for cluster effect in children, cephalosporin use during the two months before the swab was again associated with a borderline increase in penicillin-resistance (OR 1.93, 95% CI 0.93-3.98, p=0.08) (Appendix 6.4).

The point estimate of having penicillin-resistant pneumococcal isolates was greater than 1 for cephalosporin use alone during the 0-2 months and about 1 for the use during the 3-6 months before the time of swab collection (Figure 6.4). Apart from a slight rise in odds ratio for exposure 7-8 months before swabbing, the pattern of association was similar to that of any beta lactam use (Figure 6.2) and penicillin group use alone (Figure 6.3). The smaller sample size of exposed isolates resulted in a very wide confidence interval, which is difficult to plot in the graph. In figure 6.4, therefore, I limited the association up to 16 months before swab, to be consistent with Figure 6.3. I believe the significance observed at 19-20 months is explained on other grounds.

Figure 6.4: Odds of penicillin-resistance for children with exclusive cephalosporin use at different periods before swab collection, adjusted for repeated pneumococci from the same child



Multivariate analysis

None of the variables (Tables 6.2-6.4) modified or confounded the effect of exclusive cephalosporin use on penicillin-resistance. Therefore, the final model was only adjusted for repeated positive swabs collected from the same child. Children who received only cephalosporin during the two months before swab were more likely to carry a penicillin-resistant isolate than the children who did not receive any beta lactam antibiotic during that period (OR 1.93, 95% CI 0.93-3.98, p=0.08) (Appendix 6.4).

6.3.4. Effect of combined use of penicillin group and cephalosporin on the isolation of penicillin-resistant pneumococci

Univariate analysis

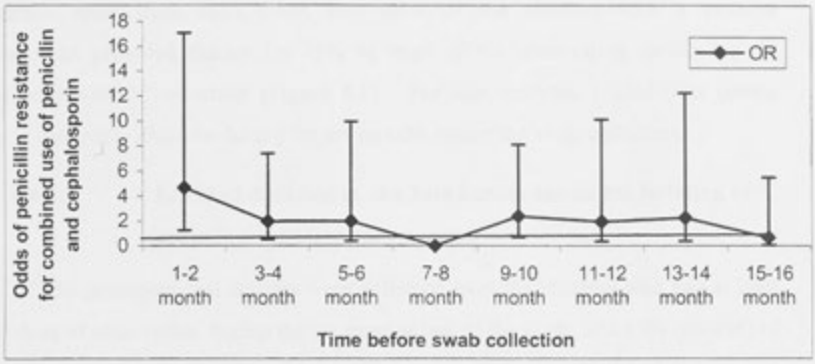
The risk of penicillin-resistance for the isolates collected from the children who received both penicillin group and cephalosporin in different periods before the swab collection was examined against those who did not receive any beta lactam antibiotics (Table 6.11). A total of 10 isolates were collected from the children who received both penicillin group and cephalosporin during the 0-2 months before the swab collection. Eight of the 10 children had suffered from one or more ear episodes either alone or with some other respiratory episodes during the two-months period. These children received a total of 97 days of penicillin group and 73 days of cephalosporin during the period. Children usually received one of the two antibiotics on most of the above days except for three days when both penicillin group and cephalosporin were used on the same day. Interestingly, 8 of the 10 children received cephalosporin before penicillin group, whereas the opposite might have been expected. The risk of penicillin-resistance was three times higher for the combined use of both antibiotics during the preceding two months compared to no beta lactam use during the period (Table 6.11).

Table 6.11: Crude relative risk of penicillin-resistance among the isolates that were exposed to both penicillin group and cephalosporin compared to those that were not exposed to any beta lactam antibiotics in each period

Time before swab collection (months)	Penicillin-resistant isolates/total isolates with both beta lactams	Penicillin-resistant isolates/total isolates with no beta lactam	RR	P (2 sided Fisher's exact p)
0-2	4/10	53/424	3.2	0.01
3-4	3/13	54/407	1.7	0.31
5-6	2/8	50/349	1.7	0.40
7-8	0/7	45/293	0	
9-10	4/13	40/253	1.9	0.16
11-12	2/8	32/217	1.7	0.43
13-14	2/7	23/151	1.9	0.34
15-16	1/9	23/143	0.7	0.69
17-18	2/4	23/125	2.7	0.12
19-20	0/1	9/75	0	
21-22	0/0	11/55	0	
23-24	1/2	3/17	2.8	0.29

The effect of combined penicillin group and cephalosporin use on penicillin-resistance was adjusted for cluster of repeated pneumococcal isolates from the same child. Children who received both penicillin group and cephalosporin during the two months before swab collection were more likely to carry a penicillin-resistant isolate than those who did not receive any beta lactam (OR 4.67, 95% CI 1.27-17.09, p=0.02) (Appendix 6.5). The numbers of total isolates and exposed isolates were not adequate to examine the effect beyond 16 months. The point estimate for penicillin-resistance was greater than 1 for combined penicillin group and cephalosporin use during most of the time periods. However, the lower number of isolates in each period resulted into wide confidence intervals around the point estimate (Figure 6.5).

Figure 6.5: Odds of penicillin-resistance for children with both penicillin group and cephalosporin use at different periods before swab collection, adjusted for repeated isolates from the same child.



Multivariate analysis

After adjusting for repeated pneumococcal isolates from the same child, the use of both penicillin group and cephalosporin during the two months increased the risk of penicillin-resistance by about 5 times (Appendix 6.5).

The summary of the analyses undertaken in Section 6.3 indicated that use of beta lactam antibiotics during the two months immediately before swab collection was significantly associated with the risk of isolation of penicillin-resistant pneumococci (Table 6.1). It also suggested that recent use is more important than use at a distant period from the swab. The effect on penicillin-resistance associated with independent penicillin group, independent cephalosporin and use of both antibiotics during the two months further suggested a dose-response effect of beta lactam use. The risk was higher for cephalosporin use alone than for penicillin group use alone (OR 1.93, 95% CI 0.93-3.98 for cephalosporin use alone and OR 1.63, 95% CI 0.66-4.01 for penicillin group use alone), but use of both antibiotics exerted a synergistic effect (OR 4.67 and 95% CI 1.27-17.09 for use of penicillin group and cephalosporin) on the isolation of penicillin-resistant pneumococci (Table 6.10).

6.4. Association of duration of beta lactam use with isolation of penicillin-resistant pneumococci

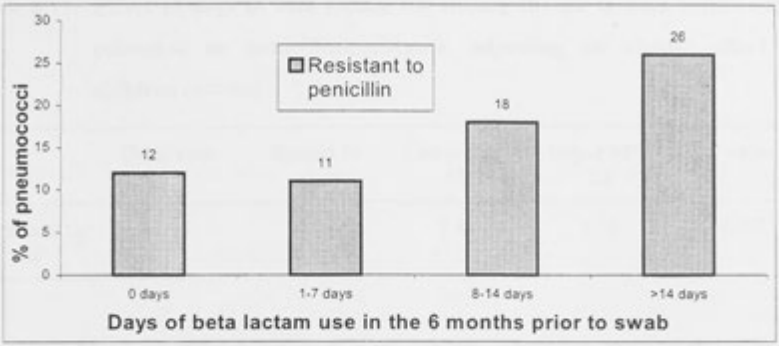
In what follows, I have explored the effect of duration of beta lactam antibiotic use on isolation of penicillin-resistant pneumococci. The swabs were collected approximately six months apart from each other, and most of the children with a positive pneumococcus provided diaries for 75% or more of the observation during the six months before swab collection (Figure 6.1). For this analysis, I used beta lactam antibiotic use by the children during the six months before the swab collection.

6.4.1. Effect of duration of any beta lactam use on the isolation of penicillin-resistant pneumococci

A total of 456 pneumococcal isolates were collected from the children who had at least 75% of days of observation during the six months before the swab, and 15% (68/456) of them were resistant to penicillin. Of the 456 isolates, 44% (199/456) had at least one day of beta lactam use and 13% (61/456) had beta lactam use for more than 14 days. The duration of beta lactam use in these children ranged from 0 to 85 days within the six months. The duration of beta lactam use during the six months was grouped into four categories on the basis of average length of an antibiotic course, which is usually seven days. The categories were: '0 days (no beta lactam)' '1-7 days (1 course)' '8-14 days (2 courses)' '>14 days (>2 courses)' (Appendix 6.6).

The percentages of penicillin-resistant isolates were equal in the group that had no beta lactam use (12%) and the group that had 1-7 days use (11%) within six months before swab; the percentage increased as the total days of beta lactam use increased beyond seven days (Figure 6.6).

Figure 6.6: Percentage of penicillin-resistance among the isolates with different beta lactam use during the six months before swab collection



I tested the association in a logistic regression model by taking cluster effect of children into account. Although the children who received beta lactam antibiotics for more than seven days within the six months before swab collection were at higher risk of carrying a penicillin-resistant pneumococcus than the children who never received beta lactam during that period, the association was statistically significant only if children had more than 14 days of beta lactam use (Table 6.12).

Table 6.12: Effect of duration of beta lactam use during the six months before swab collection on penicillin-resistance (n=456 isolates)

Days of penicillin group use in 6 months before swab	Odds ratio	Robust Std error	Lower 95% CI	Upper 95% CI	P value
1-7 days	0.86	0.37	0.37	2.02	0.73
8-14 days	1.50	0.55	0.73	3.06	0.27
>14 days	2.50	0.84	1.30	4.82	0.006

The association between duration of beta lactam use and penicillin-resistance was further explored by using duration of use as a continuous variable rather than categorising it. I used a logistic regression model in STATA that allowed adjustment for the effect of clustering within children. For each single-day increase in beta lactam

use during the six months before the swab collection, the risk of a child carrying a penicillin-resistant pneumococcus increased by 4% (Table 6.13).

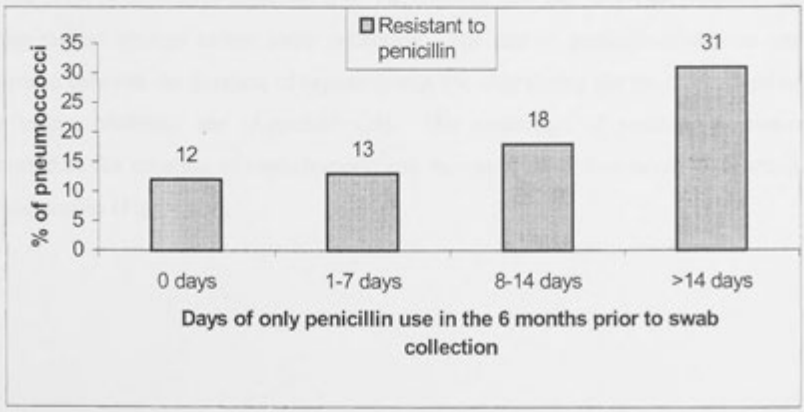
Table 6.13: Effect of days of beta lactam use during the six months before swab collection on penicillin-resistance, adjusting for cluster effect of children (n=456)

	Odds ratio	Robust St error	Lower 95% CI	Upper 95% CI	P value
Beta lactam use	1.04	0.01	1.01	1.06	0.001

6.4.2. Effect of duration of penicillin group use alone on the isolation of penicillin-resistant pneumococci

Of the 199 pneumococcal isolates collected from the children who received a beta lactam antibiotic during the six months before swab collection, 38% (76/199) had only penicillin group use. The duration of penicillin group use in these children ranged from one to 45 days during the six months. The rate of penicillin-resistance was compared against the duration of penicillin group use alone with no beta lactam use (Appendix 6.7). The rate of penicillin-resistance increased as the duration of penicillin group use increased within the six months (Figure 6.7).

Figure 6.7: Percentage of penicillin-resistant pneumococci among the isolates with different duration of only penicillin group use during the six months before swab collection



After adjusting for the cluster effect of repeated swabs from the same child, there was a dose-response effect observed in the association of penicillin group use alone with isolation of penicillin-resistant pneumococci (Table 6.14). Children who received penicillin group alone for more than 14 days within the six months before the date of swab collection were more likely to carry penicillin-resistant pneumococci (OR 3.20, 95% CI 1.10-9.27, p=0.03) (Table 6.14).

Table 6.14: Effect of duration of penicillin group use alone during the six months before swab collection on penicillin-resistance, adjusted for cluster effect of repeated pneumococcal isolates from the same child

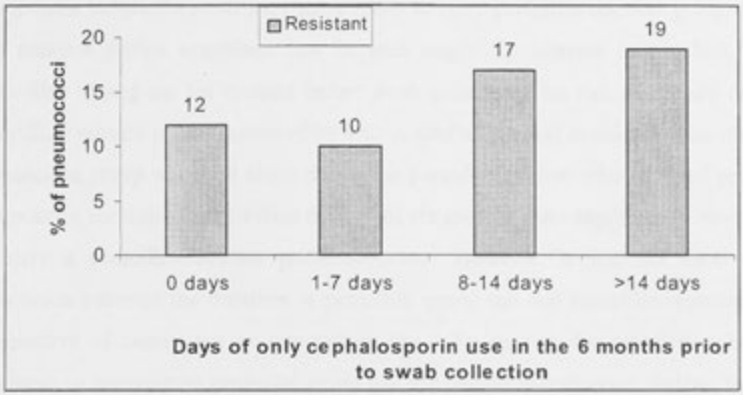
Duration of penicillin group use in 6 months	OR	Robust Std error	Lower 95% CI	Upper 95% CI	P value
1-7 days	1.00	0.57	0.33	3.05	0.99
8-14 days	1.53	0.82	0.53	4.40	0.43
>14 days	3.20	1.74	1.10	9.27	0.03

Duration of penicillin group use within the six months before swab collection was also tested as a continuous variable against penicillin-resistance. For a single increase in days of penicillin group use alone during the six months, the risk of a child carrying a penicillin-resistant pneumococcal isolate increased by 4% (OR 1.04, 95% CI 1.00-1.09, p=0.03) (Appendix 6.8).

6.4.3. Effect of duration of cephalosporin use alone on the isolation of penicillin-resistant pneumococci

A total of 86 isolates were collected from the children who had only cephalosporin use during the six months before swab collection. The rate of penicillin-resistance was compared between the duration of cephalosporin use only during the six months and no beta lactam antibiotic use (Appendix 6.9). The percentage of penicillin-resistance increased as the duration of cephalosporin use increased more than seven days within the six months (Figure 6.8).

Figure 6.8: Percentage of penicillin-resistant pneumococci among the isolates with different duration of cephalosporin-only use during the six months before swab collection



After adjusting for repeated pneumococcal isolates collected from the same child, a dose-response effect was observed similar to that observed with any beta lactam use and penicillin group use alone (Table 6.15).

Table 6.15: Effect of duration of cephalosporin use alone during the six months before swab collection on penicillin-resistance, adjusted for cluster effect of repeated pneumococcal isolates from the same child (n=343 pneumococcal isolates)

Duration of cephalosporin use in 6 months	OR	Robust Std error	P value	Lower CI	Upper CI
1-7 days	0.78	0.49	0.69	0.23	2.67
8-14 days	1.49	0.68	0.38	0.61	3.67
>14 days	1.62	1.09	0.47	0.44	6.02

6.5. Effect of number of penicillin courses on the isolation of penicillin-resistant pneumococci

The analysis suggested that children who used any beta lactam antibiotics during the two months before the swab were more likely to carry penicillin-resistant pneumococci. The analysis further suggested that for each single-day increase in any beta lactam antibiotics during the six months before swab collection, the risk of a child carrying penicillin-resistant isolate increased by 4%. A similar increase in risk was also observed if penicillin group was used alone during the period. Children who received penicillin group alone for more than 14 days during the six months were significantly more likely to carry a penicillin-resistant pneumococcus. However, it was not clear if this association between the duration of penicillin group use and penicillin-resistance was irrespective of continuous or intermittent use. To explore the association between continous or intermittent penicillin group use and penicillin-resistance, isolates from the children who received only penicillin group during the six months before swab were considered.

Of the 456 pneumococcal isolates with at least 75% of the six months observed, 76 had only penicillin group use during the period. The duration of penicillin group use for these 76 isolates ranged from one day to 45 days. A penicillin course was defined as penicillin group use for two or more consecutive days and if there was a gap of even a day, I considered it a new course. There was only one day of penicillin group use during that period associated with one isolate; I excluded that isolate from the following analysis. Of the remaining 75 isolates, 55 (73%) had only one course and 7 (9%) had more than two courses during the six-months period. The percentage of penicillin-resistance increased with increase in number of penicillin courses used in that period (Table 6.16).

Table 6.16: Percentage of penicillin-resistance among the four groups, grouped by the number of penicillin courses used during the six months before swab collection (n=75 pneumococcal isolates)

Penicillin sensitivity	1 course (% within column)	2 courses (% within column)	>2 courses (% within column)
Total	55	13	7
Sensitive	47 (85)	10 (77)	4 (57)
Resistant	8 (15)	3 (23)	3 (43)

After adjusting for repeated pneumococci isolated from the same child, there was a dose-response effect observed between the number of penicillin courses used within the six months before the time of swab collection and the isolation of penicillin-resistant pneumococci (Table 6.17). Children who used more than two penicillin courses during the six months were 4.4 times more likely to carry penicillin-resistant pneumococci; however, the association was not statistically significant (Table 6.17).

Table 6.17: Odds of penicillin-resistance for different groups, grouped by the number of penicillin courses used during the six months before the swab collection and adjusted for the repeated pneumococci isolated from a child (n=75 pneumococcal isolates)

Number of penicillin courses in 6 months (1 course referrent)	OR	Robust std error	Lower 95% CI	Upper 95% CI	P value
2 courses	1.76	1.34	0.40	7.85	0.46
>2 courses	4.41	4.11	0.71	27.40	0.11

Although the rate of penicillin-resistance increased with increase in number of penicillin courses during the six months, the duration of use might affect this association. The duration of penicillin group use was longer in isolates with more than one penicillin course than in isolates with only one course (mean 21 days and sd 9.9 days versus mean 7 days and sd 2.9 days) during the six-months period. We already established that the risk of a child to carry penicillin-resistant pneumococci increased with each day increase in the duration of penicillin group use alone during the six months, and children who

received penicillin group alone for more than 14 days within the six months were significantly more likely to carry penicillin-resistant pneumococci (OR 3.20, 95% CI 1.10-9.27, p=0.03). Therefore, I further explored if the duration of use affected the relationship between number of penicillin courses used by the children and the rate of penicillin-resistance. Most of the single penicillin courses (98%) were 2-14 days long, and 75% of the isolates with more than 14 days of penicillin group use received two or more penicillin courses (Table 6.18).

Table 6.18: Length versus duration of penicillin courses (n=75 pneumococcal isolates)

Duration of penicillin group use in 6 months	1 penicillin course in 6 months	>1 penicillin courses in 6 months
Total	55	20
2-14 days	54 (98)	5 (25)
>14 days	1 (2)	15 (75)

The distribution of penicillin-resistant isolates was different in the groups depending on the number and duration of penicillin courses (Table 6.19).

Table 6.19: Distribution of penicillin-resistant isolates among the groups, grouped by number of penicillin courses and duration of penicillin group use within six months before the time of swab collection (n=75 pneumococcal isolates)

Penicillin sensitivity	2-14 days of penicillin group use in 6 months		>14 days of penicillin group use in 6 months	
	1 course	>1 course	1 course	>1 course
	Number (%)	Number (%)	Number (%)	Number (%)
Sensitive isolates	46 (85)	4 (80)	1 (100)	10 (67)
Resistant isolates	8 (15)	1 (20)	0 (0)	5 (33)

Among the isolates that had 2-14 days of penicillin group use during the six months, the isolates that had more than one course had higher resistant isolates (20% versus 15%)

compared to those with only one course. There was only one isolate that had one penicillin course within six months with a duration of more than 14 days, which was sensitive to penicillin. However, 33% of the pneumococcal isolates that had penicillin group use of more than 14 days duration with more than one course within the six months were resistant to penicillin.

6.6. Complete versus incomplete penicillin course and the isolation of penicillin-resistant pneumococci

Thirty pneumococcal isolates had a penicllin course of 1-7 days duration. I grouped the 30 penicillin courses into an 'incomplete course (1-4 days) and a 'complete course' (5-7 days). Twenty-five per cent of the isolates collected from the children who had an incomplete penicillin course carried a penicillin-resistant isolate compared to 5% of the isolates from children who had a complete penicillin course (Table 6.20). However, there was only one isolate with a complete course that was resistant. Therefore, it was difficult to draw a conclusion from this finding.

Table 6.20: Percentage of penicillin-resistance among the isolates with complete and incomplete penicillin course (n=30 pneumococcal isolates)

Penicillin sensitivity	Incomplete course Number (%)	Complete course Number (%)	P value
Total	8	22	
Sensitive isolates	6 (75)	21 (95)	0.10
Resistant isolates	2 (25)	1 (5)	

Overall, the analysis in this section suffered from very small sample size and a definite conclusion could not be reached from this analysis.

6.7. Effect of prophylactic antibiotic use on the isolation of penicillin-resistant pneumococci

Six children received antibiotics for more than half of the observation days before the corresponding swab collection. Three of these children did not have a positive pneumococcal swab. A total of 11 swabs were collected from the other three children and a positive pneumococcus was isolated from six swabs. These children had been receiving prophylactic antibiotics for kidney reflux; one of them received cephalosporin and the other two received cotrimoxazole as prophylaxis. Three pneumococci were isolated from the child who received cephalosporin prophylaxis; two of them were resistant to both penicillin and cotrimoxazole. Another three pneumococci were isolated from the children with cotrimoxazole prophylaxis; all of them were resistant to five of the six antibiotics tested except cefotaxime. All the six isolates were resistant to at least one antibiotic and 83% (5/6) were resistant to more than one antibiotic (Table 6.21).

Table 6.21: Sensitivity status of the six isolates, isolated from the children who had prophylaxis

	Total (%) n=6
Resistant to at least one antibiotic	6 (100)
Resistant to penicillin	5 (83)
Resistant to cotrimoxazole	5 (83)
Resistant to erythromycin	4 (67%)
Resistant to tetracycline	3 (50%)
Resistant to chloramphenicol	2 (33)
Resistant to cefotaxime	0 (0)

6.8. Discussion

The data allowed me to explore three theories about the association between antibiotic use and pneumococcal antibiotic-resistance: first, that antibiotic use is associated with antibiotic-resistance; second, that greater antibiotic use will increase the likelihood of pneumococcal antibiotic-resistance; third, that the use of a broad-spectrum antibiotic is more likely than narrow-spectrum antibiotic use to be associated with a high rate of antibiotic-resistance in pneumococci.

These theories, however, have not previously been tested in prospective human studies. An association between antibiotic use and pneumococcal penicillin-resistance has been reported in a number of cross-sectional human studies. I am unaware of any similar study where a group of individuals were followed for a time period to establish this association between beta lactam use and penicillin-resistance in pneumococci. In this study, a total of 502 children were followed up for 25 months and antibiotic use by these children was monitored in detail, together with duration and reason for use. Antibiotic-resistance of nasally carried pneumococci in these children was also monitored four times during the period.

The first theory has been supported by my findings. Any beta lactam antibiotic use during the two months before swab collection was associated with a significant increase in the isolation of penicillin-resistant pneumococci (OR 2.03, 95% CI 1.15-3.56, p=0.01). Although this association was also evident for beta lactam use during the six months before swab collection with an odds ratio of greater than one, statistical significance was only achieved for use in the two months immediately before the swab. The declining sample size after two months reduced the capacity to attain statistical significance. A study with a larger sample size might further explore this association.

The second theory was also firmly supported in this study. For each day increase in beta lactam use during the six months before the swab collection, the risk of a child carrying a penicillin-resistant isolate increased by 4% (OR 1.04, 95% CI 1.01-1.06, p=0.001). In fact, children who used beta lactam antibiotics for more than 14 days during the six months before swab collection were significantly more likely to carry a penicillin-resistant pneumococcus than the children who did not use any beta lactam antibiotic during the period (OR 2.50, 95% CI 1.30-4.82, p=0.006). This association was also true when penicillin group use alone was considered. The results support the theory that the

more the bacteria carried by children are exposed to an antibiotic, the greater the likelihood that the organism will be selected for developing resistance to that antibiotic.

The results also support the third theory but are not statistically significant. Cephalosporin use alone during the two months before swab collection was associated with higher risk of penicillin-resistance (OR 1.93, 95% CI 0.93-3.98, p=0.08) than use of penicillin group only (OR 1.63, 95% CI 0.66-4.01, p=0.29). However, the risk difference between the two antibiotics did not achieve statistical significance.

I also explored the effect of incomplete antibiotic courses on carriage of penicillin-resistant pneumococci. Twenty-five per cent of the pneumococcal isolates collected from the children who had an incomplete course of penicillin of 1-4 days long, were resistant to penicillin, compared to 5% of the isolates collected from the children who had a completre course of 5-7 days long (Table 6.20). However, the difference was not statistically significant.

Finally, the study brought to light some important implications for prophylactic antibiotic use. Three pneumococcal positive swabs were isolated from a child who received cephalosporin for 520 days as a prophylaxis for urinary reflux and two of them were resistant to both penicillin and cotrimoxazole. The other isolate was not resistant to penicillin, but was resistant to erythromycin. The isolates received from the two children who received cotrimoxazole as prophylaxis were resistant to penicillin and other antibiotics tested except cefotaxime. Thus, all six isolates from these children reveal evidence of antibiotic-resistance.

The evidence from this prospective study is clear and consistent. Use of beta lactam antibiotic increases the probability of carriage of penicillin-resistant pneumococci in the short term. A reduction in the rate of prescription of beta lactam antibiotics in childhood would probably arrest the rate of growing antibiotic-resistance. If it can be shown that the heavy use of antibiotics in childhood infections is not producing discernible benefits to the recipients, the case for greater conservatism in antibiotic use is even clearer.

Chapter 7 Effects of antibiotic use on respiratory illness

7.1. Overview

This chapter explores the effects of antibiotic treatment on the respiratory illness episodes in children that presented to a doctor. Parents reported daily on the presence of 12 respiratory symptoms in their children over the study period: these 12 symptoms were used to define a respiratory episode. I calculated the duration and the total number of symptoms in an episode using them as measures of severity.

To answer the question 'Does the use of antibiotics in these episodes make a difference to the severity of illness?', I selected for study 981 respiratory episodes which resulted in one or more doctor visits in the children in the 'late-intervention group' during the period September 1997 to February 1999. Neither doctors nor parents in this group had been exposed to the clinical practice guidelines during the period. I classified all episodes into a 'less severe' and a 'more severe' group. Then I compared episodes which received antibiotics with those that did not. I performed the univariate analysis in SPSS and multivariate analysis by using a multiple linear regression model in STATA.

7.2. Definition of respiratory episode

Parents reported the presence of 12 respiratory symptoms and signs in a daily diary. These were: runny nose, blocked nose, green nasal discharge, dry cough, cold, moist cough, wheeze, sore throat, hoarse voice, earache, ear discharge, and fever.

An episode was defined as the occurrence of at least two consecutive days of any of the above reported symptoms. The end of an episode was defined as the occurrence of at least two symptom-free days. Duration of an episode was calculated from the onset of symptoms to the last day on which symptoms occurred before the occurrence of two symptom-free days. This approach to definition of a respiratory episode has previously been used by Samet et al. in a study of nitrogen dioxide and respiratory illness in infants.[155] Samet used only five symptoms to define a respiratory episode which included runny or stuffy nose, dry cough, wet cough, wheeze or trouble breathing. I included seven other symptoms and signs (green nasal discharge, earache, ear discharge, sore throat, hoarse voice, cold and fever) to define episodes.

7.2.1. Types of respiratory episode

The 12 symptoms and signs were allocated to one of the four groups: ear symptoms, throat symptoms, lower respiratory and upper respiratory symptoms. Ear symptoms included earache and ear discharge. Throat symptoms were sore throat and hoarse voice. Moist cough and wheeze constituted lower respiratory symptoms and runny nose, blocked nose, green nasal discharge, dry cough and cold were included as upper respiratory symptoms.

The episodes were classified into five types depending on the type of symptoms present in the episode (Table 7.1). The types were ear episode, throat episode, lower respiratory, upper respiratory and fever episodes. The order of classification was based on the severity and on the rate of antibiotic prescribing.[1,64] Among the acute respiratory infections, the highest antibiotic prescribing was suggested for ear illnesses and the lowest was for upper respiratory illnesses. The presence of fever in the absence of any other sign or symptom was kept as a separate category, because it could be due to any of the other four types of episodes or even due to a non-respiratory illness.

The presence of at least one day of earache or ear discharge during an episode was considered as an ear episode. If there was no ear symptom, but a throat-related symptom (sore throat or hoarse voice) was present in an episode, the episode was considered as a throat episode. Presence of at least one day of moist cough or wheeze in the absence of an ear-or throat-related symptom was considered as a lower respiratory episode. If the episode did not contain any of the ear or throat or lower respiratory symptoms, but contained one of the upper respiratory symptoms, the episode was an upper respiratory episode. If an episode consisted of only fever and was not included in either of the above classifications, then the episode was considered as a 'fever only' episode.

Table 7.1: Classification of respiratory episodes

Type of episode	Primary symptoms in association with any other symptoms
Ear episode	Earache or discharge
Throat episode	Sore throat or hoarse voice in absence of ear symptoms
Lower respiratory episode	Moist cough or wheeze in absence of ear and throat symptoms
Upper respiratory episode	Upper respiratory symptoms in absence of ear, throat and lower respiratory symptoms
Fever episode	Only fever, in absence of any other symptom

7.3. Inclusion criteria

For this part of the study, I included the data received from the children of the late-intervention group during the period from September 1997 to February 1999. Clinical practice guidelines for acute respiratory infections were given to the GPs and the parents of the early-intervention group during May 1998 (Chapter 3). Since this intervention was not blinded, it had the potential to create a bias in reporting of symptoms by parents. To eliminate such bias, analysis of the effect of antibiotics on morbidity was restricted to the data received from the late-intervention group only. The children in the late-intervention group experienced a total of 2,653 respiratory episodes during the period between September 1997 and February 1999.

Of the 2,653 respiratory episodes, 63% (1,672/2,653) did not have a visit to a doctor or to a hospital during the episode (visit). Among the remaining 981 episodes with at least one visit during an episode, the number of visits ranged from one to eight within an episode. The duration and the number of symptoms in an episode varied with the number of visits within an episode (Table 7.2).

Table 7.2: Episode characteristics grouped by the number of visits in an episode

	No visit	1 visit	2 visits	>2 visits
Total	1672	670	212	99
Type of episode				
Fever only	60 (4%)	31 (5%)	7 (3%)	1 (1%)
Upper	980 (59%)	147 (22%)	28 (13%)	3 (3%)
Lower	365 (22%)	177 (26%)	53 (25%)	18 (18%)
Throat	131 (8%)	142 (21%)	43 (20%)	16 (16%)
Ear	136 (8%)	173 (26%)	81 (38%)	61 (62%)
Total length				
Mean ±SD	7 days±5	10 days±8	15 days±11	26 days±18
Median	5 days	9 days	12 days	20 days
Total symptoms				
Mean ±SD	11±12	21±17	33±24	65±49
Median	7	18	28	50
Symptoms/day				
Mean ±SD	1.6±0.7	2.0±0.8	2.1±0.8	2.5±0.8
Median	1.4	1.9	2.2	2.5
Antibiotic use	77 (5%)	324 (48%)	127 (60%)	88 (89%)

Antibiotic use was minimal in the episodes that did not have a visit to a medical practitioner. However, there were 77 episodes that received antibiotics without a reported visit; 34 of these episodes were in children who had been receiving prophylactic antibiotics during that period. I did not have any information about the acquisition of antibiotics in the rest of the episodes without a visit. It might be that either the parent did not report a visit or used antibiotics left over from a previous prescription.

The episodes that were associated with at least one visit in an episode were considered for analysis. Since a prescription is needed in Australia to obtain antibiotics, it was necessary to restrict the analysis to those episodes involving at least one visit to a medical practitioner. This allowed a comparison to be made of severity up to the doctor visit and the subsequent use or non-use of antibiotics. Therefore I excluded from the analysis 1,672 episodes with no visit in an episode.

A total of 981 episodes had at least one visit during the episode. Of the 981 episodes, 68% (670/981) had only one visit in an episode. The episodes with only one visit were less severe in duration and number of symptoms in the episode than the episodes that had more than one visit (Table 7.2). In fact, the higher the number of visits in an episode, the more severe the episode was: mean symptoms/day was 2.0 for episodes with one visit, 2.1 for episodes with two visits, 2.5 for episodes with more than two visits (Table 7.2).

Since the episodes with only one visit constituted the major portion of respiratory episodes in the children, and also those episodes were less severe than the others, I decided to analyse those episodes separately. I therefore grouped all the respiratory episodes with at least one visit into 'less severe' (episodes with only one visit) and 'more severe' episodes (episodes with more than one visit). To have a valid estimate of the effect of antibiotics on respiratory illness, I performed analysis on the less severe and the more severe episodes separately.

7.4. Effect of antibiotics on less severe episodes

The children had a total of 670 less severe respiratory episodes during the 18 months. These episodes were associated with a single visit and 48% of the episodes received an antibiotic prescription.

7.4.1. Methods of statistical analysis

Data from the daily diary recorded by the parents, parent questionnaires and GP questionnaires were entered into an Access data base. Univariate analyses were performed in SPSS and multivariate analyses were performed by using STATA to address the issue of cluster effect of repeated episodes in the same child.

7.4.2. Exposure variable

The exposure variable was antibiotic use during a respiratory episode, which was a dichotomous variable (antibiotic).

7.4.3. Outcome variable

Severity was measured as the average number of symptoms per day from the point of visit up to the end of the episode (severity). The average number of symptoms in a day was calculated by dividing the total number of symptoms after the visit by the duration of the episode after the visit. The data collected for this variable were continuous. The distribution of severity was positively skewed. The episodes had a mean of two symptoms (standard deviation 0.8) in a day after the visit. To make the distributions more symmetrical, the average number of symptoms per day after the visit were log transformed and used as the outcome variable.

7.4.4. Selection of the model

My goal was to obtain a valid estimate of the effect of antibiotic use on the severity of respiratory episodes. Therefore I selected an exposure-disease model to answer this question, using multivariate regression analysis. The appropriate multivariate model for this question was multiple linear regression, as the outcome variable 'severity' (average number of symptoms per day after the first visit) was a continuous variable. However, I performed descriptive analysis before performing a multivariate analysis.

7.4.5. Descriptive analysis

Of the 670 respiratory episodes that were associated with only one visit during the episode, 48% (324/670) received antibiotics. The severity of the entire episode was no different between those treated with an antibiotic and those not treated, in respect to total length and total number of symptoms present in an episode (Table 7.3). The episodes that received an antibiotic prescription were more severe before the visit than the other group: average symptoms per day were 2.24 for antibiotic-treated episodes and 2.08 for episodes with no antibiotic (Table 7.3). However, after the visit, the severity was not significantly different between the two groups (Table 7.3).

Table 7.3: Comparison of severity between the episodes that received antibiotics and those that did not (n=670 episodes)

	Total length (mean)	Total symptoms (mean)	Symptoms/day (mean)
Entire episode			
Antibiotic group (n=324)	10	20.87	2.03
Non-antibiotic group (n=346)	10	20.92	1.92
*P value	0.78	0.81	0.09
Episode before visit			
Antibiotic group (n=324)	5.11	11.16	2.24
Non-antibiotic group (n=346)	5.21	10.79	2.08
*P value	0.49	0.72	0.02
Episode after visit			
Antibiotic group (n=324)	4.86	9.71	1.74
Non-antibiotic group (n=346)	5.29	10.13	1.57
*P value	0.62	0.39	0.06

*Difference between antibiotic and non-antibiotic episodes by the Mann-Whitney test

To determine the effect of antibiotics on severity, I measured the severity of the episode after the visit where the first antibiotic was prescribed in an episode.

7.4.6. Adjustment for clustering

The characteristics of an episode in a child are not necessarily independent of characteristics of other episodes in the same child. Therefore the episodes experienced by the same child cannot be regarded as independent regarding severity of illness. I used a random effect linear regression model in STATA that allowed adjustment for the impact of clustering within a child by estimating robust estimate of coefficient and standard errors. The robust estimator relaxes the assumption of independence of the observations by producing corrected standard errors for correlated observations within a child.

The command I used in STATA for linear regression was:

regress severity antibiotic, cl(idno)

severity=logarithm of average number of symptoms per day after the visit up to the end of the episode

antibiotic=episode associated with antibiotic use

cl(idno)=clustered by child identification number (adjust for multiple episodes from the same child)

Univariate analysis taking cluster effect of children

After adjusting for multiple episodes in the same child, there was no difference in severity after the first doctor visit between the antibiotic-treated episodes and the episodes that were not treated with antibiotics. The episodes that were treated with antibiotics had 4% more symptoms per day after the doctor visit than the episodes that were not treated with antibiotics (coeff=0.042, p=0.25) (Table 7.4).

Table 7.4: Univariate analysis of severity after the first visit between episodes that were treated with antibiotics and those that were not, adjusting for the cluster effect of children

	Beta coeff	Robust st error	Lower 95% CI	Upper 95% CI	P value
Episodes associated with antibiotic	0.042	0.04	-0.03	0.11	0.25

7.4.7. Multivariate analysis

The goal of the analysis was to obtain a valid estimate of the effect of use of antibiotics in an episode on the post-doctor-visit severity of respiratory episodes, after adjusting for confounding factors. I followed the stages to develop a multivariate model suggested by Kleinbaum, where the stages are variable specification, interaction assessment and assessment of confounding.[156]

Variable specification

I selected potentially confounding variables that could be biologically associated with respiratory illness or that had been shown in previous studies to be related to respiratory illness. As the severity was measured from symptoms reported by the parents, I also considered the factors that could influence parents' reporting of severity. The variables were related to episodes, children, parents and environment (Table 7.5-8.8).

The type of respiratory episode was considered both as a confounder and as an effect modifier. Severity may be different depending on the type of episode, and antibiotics may have benefit in some types but not in others. The average number of symptoms per day before the doctor visit was included, because severity after the visit could have an association with the severity before the visit. The use of medicines other than antibiotics could confound the effect of antibiotics by changing the severity of the episodes (Table 7.5).

Child variables such as age and sex were included because of reported increased susceptibility to respiratory illness in younger children and in males.[167] Parents reported in the questionnaire if the child had any major illness which included asthma, pneumonia and bronchiolitis. The variable was included as a confounding variable because of their possible biological association with respiratory illness and antibiotic treatment (Table 7.6).

Parents' age and education were considered as possible confounders because these factors could influence reporting the severity of an illness and being prescribed antibiotics in an episode (Table 7.7).

Attendance at day-care centre increases the risk of illnesses because of crowding and transmission of organisms among children.[33] The proneness of these children to more infections may result in a greater likelihood that they will receive antibiotics. Duration of care was considered because of its biological plausibility with development of respiratory illness. The more the exposure to other children the more likely it is that the child will carry an infection (Table 7.8).

Table 7.5: Episode variables

Variable description	Form of variable
Types of episode	Categorical
	Type1=fever only
	Type2=upper respiratory
	Type3=lower respiratory
	Type4=throat
	Type5=ear
Average number of symptoms/day before visit	continuous
Duration of other medicine use (other than antibiotic) in an episode	continuous

Table 7.6: Child variables

Variable description	Form of variable
Sex of child	Dichotomous
	M=0, F=1
Age of child at the start of trial	Continuous
Any major illness	Dichotomous
	No=0, yes=1

Table 7.7: Parent characteristics

Variable description	Form of variable
Age of father in years	Continuous
Age of mother in years	Continuous
Education of father	Categorical
	Father1=high school or less,
	Father2=Trade or TAFE,
	Father3=Uni graduate, father4=Postgraduate
Education of mother	Categorical
	Mother1=high school or less,
	Mother2=Trade or TAFE,
	Mother3=Uni graduate,
	mother4=Postgraduate

Table 7.8: Environmental variables

Variable description	Form of variable
Type of child care during the day	Categorical
	Care1=parent/private care
	Care2=Family day-care
	Care3=Day-care centre
Duration of care outside home (hour/week)	Categorical
	1=no care
	2=1-20 hours
	3=21-40
	4=>40
Having sibling or not	Dichotomous
	No=0. Yes=1

Interaction assessment

I assessed interaction before assessing confounding. The variables (Table 7.5-Table 7.8) were tested to determine if there was any effect modification involved with any of the variables. I included an interaction term between antibiotic use and each variable in the model between exposure, outcome and all potential confounders. I considered keeping

an interaction term in the model if the impact of the interaction term was significant at the level of $p<0.05$ by Wald test (Table 7.9).

Table 7.9: Impact of interaction by Wald test on model with all variables

Interaction terms	p value in Wald test
Antibiotic*types of respiratory episode	0.61
Antibiotic*symptom/day before first visit	0.20
Antibiotic*sex of child	0.42
Antibiotic*age of child	0.19
Antibiotic*any major illness of child	0.07
Antibiotic*age of father	0.30
Antibiotic*age of mother	0.26
Antibiotic*father's education	0.11
Antibiotic*mother's education	0.81
Antibiotic*type of day-care	0.63
Antibiotic*duration of day-care	0.52
Antibiotic*number of sibling	0.40

None of the interaction terms appeared to be significant at the level of $p<0.05$ by the Wald test.

Assessment of confounding

I assessed the potential confounders to determine if the presence of a variable distorted the relationship between the explanatory variable (antibiotic) and the outcome (severity) (Tables 7.10-7.13). I used linear regression to assess confounding by adjusting for the cluster effect of repeated episodes in the same child. At first I fitted a linear regression model with only the explanatory variable against the outcome and calculated a crude beta-coefficient of severity associated with antibiotic use against no antibiotic use. The crude coefficient was 0.042. Then the same calculation was done adding one potential confounder in the model at a time. The resulting beta coefficient was compared with the crude beta-coefficient to determine if the variable was a confounder. A distortion of coefficient over 10% (<0.038 or >0.046) was considered as a meaningful change. The results of the assessment of confounding are shown in Tables 8.11-8.14. For example, adding type of episode in the model resulted in a coefficient of 0.004, which was more

than a 10% distortion from the crude coefficient (Table 7.10). Therefore, I accepted that the type of episode confounded the relationship between antibiotic use and severity.

Table 7.10: Evaluation of episode variables for distortion of effect of antibiotic use on severity

Variables	B coeff	Interpretation
Crude co-efficient	0.042	
Adjusted for types of episode	0.005	Confounder
Adjusted for number of symptoms/day before first visit	0.006	Confounder
Adjusted for duration of other medicine use	0.045	*Not confounding

*not confounding because beta coefficient did not alter 10% from.042.

Table 7.11: Evaluation of child variables for distortion of effect of antibiotic use on severity

Variables	B coeff	Interpretation
Crude co-efficient	0.042	
Adjusted for sex of child	0.055	Confounder
Adjusted for age of child	0.050	Confounder
Adjusted for major illness	0.056	Confounder

Table 7.12: Evaluation of parent variables for distortion of effect of antibiotic use on severity

Variables	B coeff	Interpretation
Crude co-efficient	0.042	
Adjusted for age of father	0.053	Confounder
Adjusted for age of mother	0.050	Confounder
Adjusted for father's education	0.047	Confounder
Adjusted for mothers education	0.053	Confounder

Table 7.13: Evaluation of environmental variables for distortion of effect of antibiotic use on severity

Variables	B coeff	Interpretation
Crude co-efficient	0.042	
Adjusted for type of day-care	0.052	Confounder
Adjusted for duration of day-care	0.055	Confounder
Adjusted for presence of sibling	0.051	Confounder

Of the episode variables, type of respiratory episode and average number of symptoms per day before first visit meaningfully distorted the relationship between antibiotic use and severity. Most of the variables related to children and parents also confounded the relationship between antibiotic use in an episode and the severity of the episode.

Final model

The final multivariate model thus contained 12 confounders and allowed for the cluster effect of children. The coefficients for the dichotomous exposure variable estimate the mean difference between the logarithm of severity for antibiotic-treated episodes and for non-antibiotic episodes. After adjusting for confounding, antibiotic use in an episode did not show an association with the subsequent severity of that respiratory episode (coeff=0.008, p=0.78) (Table 7.14).

Table 7.14: Effect of antibiotic use on severity in less severe respiratory episodes, fully adjusted for confounding and the cluster effect of children (n=528 episodes)

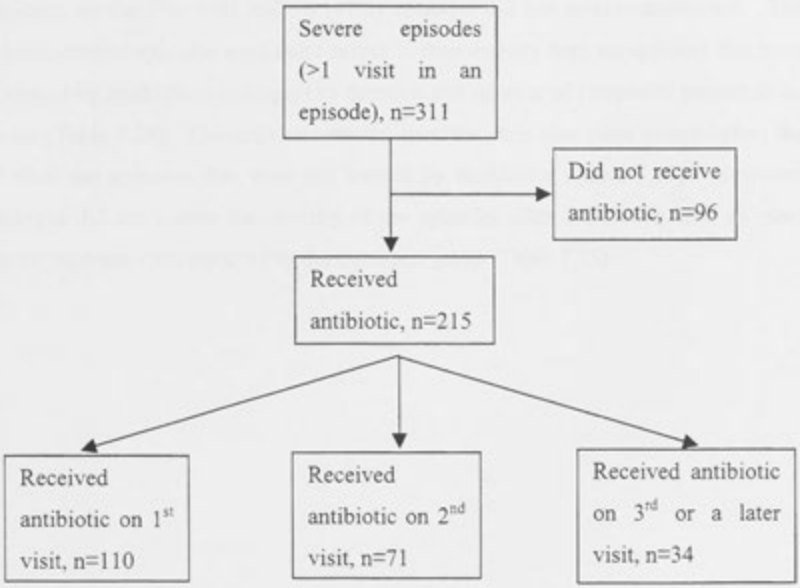
	Beta coeff	Robust* standard error	P value	Lower 95% cI	Upper 95% cI
Antibiotic use in an episode	0.008	0.027	0.78	-0.05	0.06

*Standard error adjusted for clustering episodes in the same child

7.5. Effect of antibiotics on more severe episodes

A total of 311 episodes were associated with more than one visit during the episode and 215 (69%) of these received an antibiotic. Antibiotics were prescribed at different time in different episodes (Figure 7.1).

Figure 7.1: Visit where antibiotic was prescribed in severe episodes



I performed the analysis in two stages to determine the effect of antibiotics on severe episodes. The first analysis was performed including the 96 episodes that did not receive antibiotics in the episode and the 110 episodes that received antibiotics on the first visit, and severity was measured from the first visit to the end of the episode for both groups.

Of the 96 episodes that did not receive antibiotics, 89% (85/96) had two visits in an episode. I performed the second analysis including the same 96 episodes with no antibiotic and the 71 episodes that received antibiotics on the second visit. However, this time, severity was measured from the second visit to the end of the episode for both groups. The effect of antibiotics could not be measured on the 34 episodes that received

antibiotics on the third or a later visit because of the inadequate number of comparable episodes.

7.5.1. Episodes that were treated with antibiotics on the first visit

Descriptive analysis

A total of 206 respiratory episodes were included in the analysis: 110 (53%) received antibiotics on the first visit and 96 (47%) episodes did not receive antibiotics. The antibiotic-treated episodes were more severe in their entirety than the episodes that were not treated by antibiotics, in respect to duration and number of symptoms present in an episode (Table 7.15). The antibiotic-treated episodes were also more severe before the visit than the episodes that were not treated by antibiotics (Table 7.15). However, antibiotics did not reduce the severity of the episodes after the doctor visit, as more severe symptoms were reported by the treatment group (Table 7.15).

Table 7.15: Comparison of severity between the episodes that received antibiotic and those that did not (n=206 episodes)

	Total length (mean)	Total symptoms (mean)	Symptoms/day (mean)
Entire episode			
Antibiotic group (n=110)	20	47.61	2.33
Non-antibiotic group (n=96)	15	32.83	2.04
*P value	0.002	<0.001	0.005
Episode before visit			
Antibiotic group (n=110)	5.65	13.82	2.76
Non-antibiotic group (n=96)	4.81	10.35	2.19
*P value	0.72	0.03	<0.001
Episode after visit			
Antibiotic group (n=110)	14.40	33.79	2.24
Non-antibiotic group (n=96)	10.15	22.48	2.01
*P value	0.001	0.002	0.03

*Difference between antibiotic and non-antibiotic episodes by the Mann-Whitney test

Univariate analysis taking cluster effect of children

The severity of episodes after the first doctor visit was compared between the episodes that received antibiotics on the first visit and those that did not receive antibiotics. The episodes in a child are not necessarily independent of each other. After adjusting for multiple episodes in the same child, the antibiotic treated episodes had 16% more symptoms per day after the first visit than the episodes that were not treated with antibiotic (coeff=0.16, p=0.01) (Table 7.16).

Table 7.16: Univariate analysis of severity after the first visit between episodes that were treated with antibiotics and those that were not, adjusting for the cluster effect of children (n=206 episodes)

	Beta coeff	Robust st error	P value	Lower 95% CI	Upper 95% CI
Episodes associated with antibiotic	0.16	0.06	0.01	0.04	0.27

Multivariate analysis

The impact of interaction was assessed before considering confounding. The effect of interaction was tested for the variables (Tables 7.5-7.8) with interaction with the exposure of antibiotic-treated episodes using the Wald test. Two interaction terms were significant ($p<0.05$) by this test: average number of symptoms per day before first visit, and age of mother; each interacted with antibiotic use in an episode (Table 7.17).

Table 7.17: Impact of interaction terms by Wald test on model with all variables

Interaction terms	p value in Wald test
Antibiotic*types of respiratory episode	0.66
Antibiotic*symptoms/day before first visit	0.003
Antibiotic*sex of child	0.85
Antibiotic*age of child	0.14
Antibiotic*any major illness of child	0.63
Antibiotic*age of father	0.89
Antibiotic*age of mother	0.03
Antibiotic*father's education	0.22
Antibiotic*mother's education	0.30
Antibiotic*type of day-care	0.17
Antibiotic*duration of day-care	0.27
Antibiotic*number of siblings	0.55

In the presence of interaction, confounding assessment requires subjective decisions. To avoid making subjective decisions, the safest approach is to keep all potential confounders in the model.[156] This would ensure the proper control of confounding but may lack precision.

Both of the variables (average symptoms per day and age of mother) were continuous, and therefore the overall estimate would be for a child who had no symptom before visit and whose mother is 0 years, which would not be meaningful. To have a meaningful

estimate, the variables were transformed towards central by subtracting the mean from the actual value. The mean age of mothers was 31 years and children had on average two symptoms per day before the visit. The final multivariate model contained two interaction terms: average number of symptom per day before first visit*antibiotic-treated episode, and age of mother*antibiotic-treated episode (Table 7.18).

Table 7.18: Effect of antibiotic use on more severe respiratory episodes that received antibiotics on the first visit, fully adjusted for confounding and the cluster effect of children (n=186 episodes)

	Beta coeff	Robust std error	P value	Lower 95% CI	Upper 95% CI
Antibiotic use in an episode	0.07	0.06	0.22	-.04	0.18

Antibiotic use did not change the severity even in more severe respiratory episodes that received antibiotics on the first visit.

7.5.2. Episodes that received antibiotics on the second visit

Descriptive analysis

A total of 71 respiratory episodes received antibiotics on the second visit. The severity of these episodes were compared with the 96 episodes that did not receive antibiotics even after having two or more visits in an episode. For this analysis, severity was measured from the point of second visit in the episode. The severity was greater for the entire episodes in the antibiotic-treated group than the non-antibiotic group (Table 7.19). The antibiotic-treated episodes were also more severe both before and after the second visit compared to the episodes that were not treated with antibiotics (Table 7.19).

Table 7.19: Comparison of severity between the episodes that received antibiotics and those that did not (n=167 episodes)

	Total length (mean)	Total symptoms (mean)	Symptoms/day (mean)
Entire episode			
Antibiotic group (n=71)	17	38.14	2.29
Non-antibiotic group (n=96)	15	32.83	2.04
*P value	0.16	0.06	0.05
Episode before visit			
Antibiotic group (n=71)	9.73	23.38	2.55
Non-antibiotic group (n=96)	10.27	23.30	2.23
*P value	0.68	0.19	0.05
Episode after visit			
Antibiotic group (n=71)	6.56	14.76	2.00
Non-antibiotic group (n=96)	4.69	9.53	1.44
*P value	0.007	0.005	0.002

*Difference between antibiotic and non-antibiotic episodes by the Mann-Whitney test

Univariate analysis

After adjusting for repeated episodes in the same child, the severity of the episodes after the second visit was not different between the antibiotic-treated episodes and the episodes not treated with antibiotics (Table 7.20).

Table 7.20: Effect of antibiotic on severity in episodes that were prescribed antibiotic on the second visit (n=167 episodes)

	Beta coeff	Robust std error	P value	Lower 95% CI	Upper 95% CI
Antibiotic use in an episode	0.02	0.03	0.57	-0.04	0.07

Multivariate analysis

None of the interaction terms was significant ($p<0.05$) by the Wald test. I tested confounding after interactions were assessed. A total of 10 variables meaningfully distorted the relationship between antibiotic use and severity (Table 7.21).

Table 7.21: Evaluation of variables for distortion of effect of antibiotic use on severity

Variables	B coeff	Interpretation
Crude co-efficient	0.015	
Adjusted for types of episode	-0.003	Confounder
Adjusted for symptoms/day before 2nd visit	0.006	Confounder
Adjusted for duration of other medicine use	0.016	Not confounding
Adjusted for sex of child	0.008	Confounder
Adjusted for age of child	0.007	Confounder
Adjusted for major illness	0.004	Confounder
Adjusted for age of father	0.006	Confounder
Adjusted for age of mother	0.005	Confounder
Adjusted for father's education	0.017	Not confounding
Adjusted for mother's education	0.013	Not confounding
Adjusted for type of day-care	0.010	Confounder
Adjusted for duration of day-care	0.008	Confounder
Adjusted for presence of sibling	0.008	Confounder

Final model

The final multivariate model was adjusted for 10 confounders and for cluster effect of children (Table 7.22). After fully adjusting for confounding and cluster, antibiotic use in an episode did not significantly reduce the severity of the episode after the doctor visit.

Table 7.22: Effect of antibiotic on respiratory episodes that received antibiotic on the second visit, fully adjusted for confounding and the cluster effect of children (n=134 episodes)

	Beta coeff	Robust std error	P value	Lower 95% CI	Upper 95% CI
Antibiotic use in the episode	-0.005	0.02	0.83	-0.05	0.04

7.6. Discussion

Antibiotic use did not show a beneficial effect on respiratory episodes, even when the episode was more severe. These results support the bulk of reviews that showed no beneficial effect of antibiotics on acute respiratory illness (Chapter 2). However, antibiotics are routinely prescribed for these illnesses, for example, about half of the less severe episodes and over 60% of the more severe episodes were treated with antibiotics (Table 7.2). Most of the respiratory illnesses are of viral origin and antibiotic use does not make a difference in viral illnesses. Complications from acute respiratory illness are not common in developed countries; complications from sore throat are rarely seen.[168] Complications from acute otitis media are also rare, for example, in the Netherlands, among 4,860 consecutive patients with acute otitis media who were not given antibiotics, only two experienced mastoiditis. However, both patients responded to the oral antibiotics.[66]

I could not analyse the effect of antibiotics on the episodes that received antibiotics on the third or a subsequent visit because of inadequate number of comparable episodes. If these episodes are the ones that developed complications, antibiotics could have a different effect on those.

Because of the low prevalence of complications in developed countries, antibiotics can be avoided as a routine practice for acute respiratory infections. If antibiotic use could be withheld and used only for the complicated respiratory infections, we would see a substantial reduction in antibiotic use. However, the implications will be different for developing countries, where the complications from ARI, for example, rheumatic fever and acute glomerulonephritis, are common.

Chapter 8 Discussion and conclusions

8.1. Introduction

Since the late 1960s, strains of antibiotic-resistant pneumococci have been isolated with increasing frequency around the world.[169] As penicillin has been the antibiotic of choice for pneumococcal infections, the emergence of penicillin-resistance has made the choice of empiric therapy for these infections more difficult.[95]

The collection of longitudinal data on antibiotic use and respiratory symptoms in this prospective cohort study permitted me to explore the likely effects of antibiotic use on pneumococcal antibiotic-resistance and on the outcomes of the illnesses. In view of the growing concern at the rate of increase in antibiotic-resistance, an exploration of the likely benefits and costs of reducing antibiotic use seemed to be highly desirable.

This chapter summarises the effect of antibiotic use on respiratory illness and on antibiotic-resistance in the cohort. It also discusses the limitations of the study and considers future needs in this field of work.

8.2. Use of beta lactam antibiotics was associated with an increase in pneumococcal resistance to penicillin

The primary research question was whether antibiotic use in children affects antibiotic-resistance in pneumococci. I concentrated my analysis on beta lactam antibiotic use in children and its association with pneumococcal resistance to penicillin. The study provided support for two theories of antibiotic-resistance (Chapter 6).

First, children who received a beta lactam antibiotic during the two months before swab collection were more likely to carry a penicillin-resistant pneumococcus (PRP) than children who did not (OR 2.03, 95% CI 1.15-3.56, p=0.01). Although this association was also suggestive for beta lactam use during the previous six months (Odds ratio>1), statistical significance was only reached for beta lactam use during the two months before swab collection. A study with a larger sample size would be needed to explore this association beyond two months.

Secondly, the likelihood that a child carried a resistant pneumococcus increases with an increase in duration of antibiotic use. The total beta lactam antibiotic use by the children during the six months before swab collection was evaluated against the rate of isolation of PRP. The risk of a child carrying a penicillin-resistant pneumococcus increased by 4% for each extra day of beta lactam antibiotic use during the previous six months (OR 1.04, 95% CI 1.01-1.06, p=0.001). The risk of carriage of PRP was significantly higher in children who used beta lactam antibiotics for more than 14 days during the six months compared to the children who did not receive any beta lactam (OR 2.50, 95% CI 1.30-4.82, p=0.006). This association was also true when the penicillin group of antibiotics alone was considered.

The results also suggest, but do not establish, that use of broader-spectrum antibiotics (cephalosporin) was more likely to increase penicillin-resistance than use of narrower-spectrum antibiotics (penicillin group). I found that cephalosporin use during the two months before swab collection was associated with higher risk of penicillin-resistance than the risk associated with penicillin group use (OR 1.93 versus OR 1.63). The difference was not statistically significant.

8.3. Antibiotic use did not reduce the severity of respiratory illness

The second linked question that this study aimed to answer was whether the use of an antibiotic for acute respiratory infection in children had demonstrably altered the severity of illness. Here a comparison was made between the respiratory episodes that were treated with antibiotics and the episodes that were not. The effect of antibiotic treatment was examined separately on less severe and more severe respiratory episodes. Less severe episodes had a mean of two symptoms per day, the severe episodes had a mean of 2.3 symptoms per day. Forty-eight per cent of the less severe respiratory episodes received an antibiotic compared to 69% of the more severe episodes. In the less severe group, antibiotics were prescribed more often for children who had more symptoms before the visit to the doctor (average symptoms per day 2.24 for episodes with antibiotic versus 2.08 for episodes with no antibiotic, p=0.02). However, there was no difference observed between the two groups after the doctor visit (fully adjusted beta coefficient 0.01, p=0.73). The results suggest that antibiotic use did not reduce the severity of respiratory illness in children who presented with less severe illness. There was also no demonstrable difference in outcome of severity between the more severe episodes that were or were not treated with an antibiotic (Chapter 7).

These findings cannot be seen as evidence that the use of antibiotics did not alter outcome. But they do provide some support for a more conservative approach to antibiotic use, especially when considered in conjunction with evidence from recent overviews of randomised controlled trials (Chapter 2).

8.4. Strengths and limitations of the study

The study was designed to minimise the potential problems of a cohort study. Loss to follow-up is the biggest problem for a study of this duration. We undertook a number of strategies to maintain a good participation rate.

A research assistant was employed to ring all the parents who failed to send the previous month's diary back by the middle of the following month. During each set of nasal swab collections, a research assistant and I rang every parent to remind them on the evening before the date of swab collection. This short telephone conversation actually helped both parents and us to know each other, and also helped parents to feel involved in the study. That also helped us to track the change of address and telephone number

for parents. We also sent out repeated newsletters to both parents and GPs informing them of different aspects of the study.

Notwithstanding these efforts to maintain compliance there was significant incompleteness in diary data. Therefore I had to express all the study events as days per child-year, where the number of child-days in the denominator varied across the study population. I was unable to ascertain the nature and extent of bias that resulted from this limitation; however, it is possible that the study results represent an over estimation of respiratory illness in children. As I mentioned in Chapter 5, a few parents sent a diary after a prolonged interval of non-return. At that time, we did not check the reason for recommenced diary recording: it could be an episode of illness in children which reminded parents about the diary. However, the rate of respiratory illness in the study children is still comparable with the reported rate in children in day-care centres in the ACT.[154]

Although the majority of the study GPs were recruited strictly by the protocol in primary recruitment, we could not maintain this random process during secondary recruitment. We approached one GP from each of the practices in the sample frame during primary recruitment. In the secondary recruitment we selected a few names of the GPs from group practices where another GP was approached before, but that GP declined to participate. Although only a total of five GPs were recruited in this recruitment, this subset of GP recruitment could lead to a selection bias of the sample: they might overrepresent the GPs practising in a group practice. However, the demographic details of the study GPs were representative of Australian GPs (Chapter 5). GPs practising in a group practice might prescribe fewer antibiotics because of the likelihood of dissemination of scientific information between the GPs. The lower prescribing by the GPs subsequently could affect the antibiotic-resistance level in the children. However, this factor should not affect the association of antibiotic use with antibiotic-resistance or with outcome of respiratory illness in children.

The recruitment of children took much longer than anticipated. We anticipated two weeks would be needed to recruit fifteen children from a GP's surgery. However, even after repeated reminders and encouragement from us, it took several months for most of the GPs to recruit even half of the target number of children. A consequence of the longer recruitment was a shorter period of data collection before the first round of swab

collection. Consequently only a small proportion of pneumococci isolated in the first swab could be used for the analysis of antibiotic use versus antibiotic-resistance.

Although the study was able to show a significant association between antibiotic use and antibiotic-resistance, it sometimes suffered from problems associated with inadequate sample size. For example, there was insufficient power to explore thoroughly the association between pneumococcal penicillin-resistance and beta lactam antibiotic use for the 2-6 months window before carriage of a resistant organism. For the same reason, the effect of prophylactic antibiotic use on antibiotic-resistance could not be adequately explored.

Despite these limitations, the results are consistent with current theories regarding antibiotic-resistance. The higher risk of PRP carriage associated with broader-spectrum antibiotics (cephalosporin) against narrower-spectrums (penicillin group), though suggestive, was not however statistically proved. Nor could the theory regarding complete versus incomplete antibiotic courses and antibiotic-resistance be explored sufficiently, because of the limited sample size.

Selection bias may have occurred when parents and children were selected for the study by their GPs as seen from the higher educational and income profile of the study parents. The higher socioeconomic profile of the study children could affect the generalisability of the study findings. Once an antibiotic was given to a child, the severity of illness or carriage of PRP should not differ between the children with parents having different levels of education or income. However, reporting of symptoms, thus, of the severity of illness, could be different depending on the level of parents' education. For this reason, I considered the socioeconomic variables related to parents as potential confounders in the analysis of antibiotics' effect on severity.

Recall bias is probably an issue in this study. The daily diary was sent to the parents as a monthly calendar. Parents were asked to record respiratory symptoms and treatment of their children every day. In reality, it seemed that daily completion of the diary was probably not possible for most of the parents, some parents completed the calendar at the end of each month and sometimes the recall was even longer. By that time, they could forget some symptom or treatment, especially when it was trivial. This might be an explanation for having some records of antibiotic treatment from children without a record of a medical consultation. In future work, the problem of recall bias could be

reduced by a fortnightly telephone interview with every parent along with a calendar report, which could be used as a counter check as well as a reminder.

There was a possibility that symptoms of respiratory illness and management may have been underreported. This study was a part of a RCT of clinical practice guidelines, and parents were aware that an objective of the study was to reduce doctor visits and antibiotic use in ARIs. Some parents might have tended to report fewer doctor visits. In some respiratory episodes, we found that there was abrupt disappearance of respiratory symptoms after the day of commencement of antibiotic treatment in an apparently severe episode before the doctor visit. It might well be a real effect or a coincidence; however, it might also be that some parents reported fewer symptoms after antibiotic prescription to validate antibiotic use in that episode. Parents could also have forgotten the events once the child started feeling better, or they did not feel it important to report the symptoms. A fortnightly telephone interview with parents could reduce this problem as well.

The funding for this study allowed us to test only one pneumococcal isolate from each child during each round of swab collection. We therefore tested only the predominant isolate from each child in each collection. As we could not test all pneumococcal isolates, the rate of resistance may be underreported in this study. Funding limitations meant that the pneumococcal isolates could not be serotyped. It was not therefore possible to test whether repeated pneumococcal carriage in a child was due to prolonged carriage of the same strain of pneumococci or acquisition of a new strain.

8.5. Recommendations for the future

My findings on antibiotic-resistance add to the growing evidence in the literature that decreasing unnecessary antibiotic use is the primary step to reduce the emergence of antibiotic-resistance. They also suggest that when antibiotic use is indicated, a shorter duration, adequate to eradicate the organisms is less likely to induce antibiotic-resistance. The results further suggest that treatment with a narrow-spectrum agent may be less likely to promote carriage of resistant organisms.

There is emerging evidence that antibiotics can safely be withheld in most childhood respiratory illnesses. My own analysis cannot be seen as definitive but it certainly suggests that even for the severe illnesses presented at the time of doctor visit, the respiratory outcomes were not appreciably different in the two groups, whether they were treated with or without antibiotics.

8.6. Conclusion

This study is one of the most extensive follow-up studies of the twin issues of antibiotic prescribing and pneumococcal antibiotic-resistance in childhood. The size and duration of the study created some problems of data completeness but enabled me to conclude that, in the Australian community setting:

- use of beta lactam antibiotics increases the likelihood that a child will carry penicillin-resistant pneumococcus in the following six months.
- the greater the duration of beta lactam use, the higher the likelihood of carriage of a penicillin-resistant pneumococcus in children.

Also, my comparative analysis of the clinical outcomes of antibiotic use in respiratory infections in the general practice setting strongly suggested that the high use of antibiotics was not associated with evidence of reduced morbidity, even when severity of illness at the time of presentation to the GP was controlled for. This evidence, taken in conjunction with the emerging evidence from RCTs, provides added justification for greater conservatism in the prescription of antibiotics for these ubiquitous infections.

References

1. Bridges-Webb C, Britt H, Miles DA, Neary S, Charles J, Traynor V. Morbidity and treatment in General Practice in Australia 1990-1991. *Med J Aust* 1992;157(supplement):33-42.

2. Gwaltney JM. The common cold. *Principles and practice of infectious diseases.* 3rd ed, 1990.

3. Collignon PJ, Bell-JM. Drug resistant Streptococcus pneumoniae: the beginning of the end for many antibiotics? *Med J Aust* 1996;164(2):64-67.

4. Turnidge JD, Bell JM, Collignon PJ. Rapidly emerging antimicrobial resistance in Streptococcus pneumoniae in Australia. *Med J Aust* 1999;170:152-155.

5. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996;313:387-91.

6. Brook I, Gober AE. Prophylaxis of amoxicillin or sulfisoxazole for otitis media: Effect on the recovery of penicillin resistant bacteria from children. *Clin Infect Dis* 1996;22:143-5.

7. Molstad S, Ekedahl A, Hovelius B, Thimansson H. Antibiotics prescription in primary care: a 5-year follow-up of an educational programme. *Family Practice* 1994;11:282-286.

8. Reichler MR, Allphin AA, Breiman RF, Schreiber JR, Ernold JE, McDougal LK, et al. The spread of multiply resistant Streptococcus pneumoniae at a day care center in Ohio. *J Infect Dis* 1992;166:1346-53.

9. Stansfield SK, Shepard DS. Acute Respiratory Infection. In: Jamison D, Mostly W, Measham A, Bobbabilla J, editors. *Disease control priorities in developing countries*: Oxford U.Press, 1993:67-89.

10. Berman S. Epidemiology of acute respiratory infections in children of developing countries. *Rev Infect Dis* 1991;13:454-62.

11. Campbell H. Acute respiratory infection:a global challenge. *Archives of Disease in Childhood 1995* 1995;73:281-286.

12. Berman S, McIntosh K. Acute respiratory infections. 1985.

13. Gadomski AM. Potential interventions for preventing pneumonia among young children: lack of effect of antibiotic treatment for upper respiratory infections. *Paediatr Infect Dis J* 1993;12:115-20.

14. Douglas RM, Woodward A, Miles H, Buetow S, Morris D. A prospective study of proneness to acute respiratory illness in the first two years of life. *Int J Epidemiology* 1994;23(4):818-826.

15. Coriell LL. Clinical syndromes in children caused by respiratory infection. *Med Clin N Amer* 1967;51.

16. Denny FW, Clyde WA, Jr. Acute lower respiratory tract infections in non-hospitalized children. *J Pediatr* 1986;108:635-646.

17. Krugman S, Ward R, Katz S. *Infectious diseases of children*. 6th ed. St. Louis: CV Mosby, 1977.

18. Ruuskanen O, Heikkinen T. Viral-bacterial interaction in acute otitis media. *Pediatr Infect Dis J* 1994;13:1047-9.

19. Arola M, Ruuskanen O, Ziegler T, Mertsola J, Nanto-Salonen K, Putto-Laurila A, et al. Clinical role of respiratory virus infection in acute otitis media. *Pediatrics* 1990;86:848-855.

20. Howie V, Ploussard J, Lester RJ. Otitis media: a clinical and bacteriological correlation. *Pediatrics* 1970;45:29-35.

21. Wald E, Milmoe G, Bowen A, Ledesma-Medina J, Salamon N, Bluestone C. Acute maxillary sinusitis in children. *N Engl J Med* 1981;304(13):749-754.

22. Glezen WP, Denny FW. Epidemiology of acute lower respiratory disease in children. *N Engl J Med* 1973;288(10):498-505.

23. Hall C, Powell K, Schnabel K, Gala C, Pincus P. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. *J Pediatr* 1988;113:266-271.

24. Torzillo P, Dixon J, Manning K, Hutton S, Gratten M, Hueston L, et al. Etiology of acute lower respiratory tract infection in Central Australian Aboriginal children. *Pediatr Infect Dis J* 1999;18(8):714-21.

25. Korppi M, Leinonen M, Koskela M, Makela P, Lavniala K. Bacterial coinfection in children hospitalized with respiratory syncytial virus infections. *Pediatr Infect Dis J* 1989;8:687-692.

26. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974;227(2):164-9.

27. Berman S, Duenas A, Bedoya A, Constain V, Leon S, Borrero I, et al. Acute lower respiratory tract illnesses in Cali, Colombia: a two year ambulatory study. *Pediatrics* 1983;71:210-218.

28. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol* 1989;129(6):1232-46.

29. Payling-Wright G, Payling-Wright H. Etiological factors in broncho-pneumonia amongst infants in London. *J Hyg (Camb)* 1945;44:15-30.

30. Gardner G, Frank AL, Taber LH. Effects of social and family factors on viral respiratory infection and illness in the first year of life. *J Epidemiol Community Health* 1984;38:42-48.

31. Woods H. The influence of external factors on the mortality from pneumonia in childhood and later adult life. *J Hyg (Camb)* 1927;26:36-43.

32. Monto AS, Ross H. Acute respiratory illness in the community: effect of family composition, smoking, and chronic symptoms. *Br J Prev Soc Med* 1977;31(2):101-8.

33. Strangert K. Respiratory illness in preschool children with different forms of day care. *Pediatrics* 1976;57(No.2):191-196.

34. Fleming DW, Cochi SL, Hightower AW, Broome CV. Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? *Pediatrics* 1987;79(1):55-60.

35. Hurwitz ES, Gunn WJ, Pinsky PF, Schonberger LB. Risk of respiratory illness associated with day-care attendance: a nationwide study. *Pediatrics* 1991;87(No 1):62-69.

36. Soyka LF, Robinson DS, Lachant N, Monaco J. The misuse of antibiotics for treatment of upper respiratory tract infections in children. *Pediatrics* 1975;55:552-6.

37. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office based physicians in the United States. *JAMA* 1995;273:214-219.

38. Cunningham DG, Challapalli M, O'Keefe JP, Gardner HG, Puczynski MS. Unprescribed use of antibiotics in common childhood infections. *J Pediatr* 1983;103(5):747-749.

39. Hossain MM, Glass RI, Khan MR. Antibiotic use in a rural community in Bangladesh. *Int J Epidemiol* 1982;11(4):402-5.

40. Stein CM, Todd WT, Parirenyatwa D, Chakonda J, Dizwani AG. A survey of antibiotic use in Harare primary care clinics. *J Antimicrob Chemother* 1984;14(2):149-56.

41. Lexomboon U, Duangmani C, Kusalasai V, Sunakorn P, Olson LC, Noyes HE. Evaluation of orally administered antibiotics for treatment of upper respiratory infections in Thai children. *J Pediatr* 1971;78(5):772-778.

42. McManus P, Hammond ML, Whicker SD, Primrose JG, Mant A, Fairall SR. Antibiotic use in the Australian community, 1990-1995. *Med J Aust* 1997;167:124-127.

43. Harvey KJ, Stewart R, Hemming M, Naismith N, Moulds R. Educational antibiotic advertising. *Med J Aust* 1986;145:28-32.

44. Fox JP, Hall CE, Cooney MK, Luce RE, Kronmal RA. The Seattle virus watch: II. Objectives, study population and its observation, data processing and summary of illnesses. *Am J Epidemiol* 1972;96(4):270-285.

45. Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. *Rev Infect Dis* 1990;12:S870-8.

46. Stolley PD, Lasagna L. Prescribing patterns of physicians. *J Chronic Dis* 1969;22:395.

47. McGregor A, Dovey S, Tilyard M. Antibiotic use in upper respiratory tract infections in New Zealand. *Family Practice* 1995;12:166-170.

48. Arroll B, Kenealy, T. Antibiotics versus placebo for the common cold (Cochrane Review). *The Cochrane Library*. Oxford: Update Software, 1999.

49. Ackerman BD. Treatment of undifferentiated respiratory infections in infants. *Clin Pediatr* 1968;7:391.

50. Hardy LM, Traisman HS. Antibiotics and chemotherapeutic agents in the treatment of uncomplicated respiratory infection in children: A controlled study. *J Pediatr* 1956;48:146.

51. Townsend EH, Radebaugh JF. Prevention of complications of respiratory illness in pediatric practice: A double blind study. *N Engl J Med* 1962;266:683.

52. Wald ER. Sinusitis in children. *Pediatr Infect Dis J* 1988;7:150-153.

53. Farr BM, Hendley JO, Kaiser D, Gwaltney J. Two randomized controlled trials of virucidal nasal tissues in the prevention of natural upper respiratory infections. *American Journal of Epidemiology* 1988;128(5):1162-72.

54. O'Brien KL, Dowell SF, Schwartz B, Marcy SM, Phillips WR, Gerber MA. Acute sinusitis-principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101:174-177.

55. Wald E. Management of sinusitis in infants and children. *Pediatr Infect Dis J* 1988;7:449-452.

56. Hays G, Mullard J. Can nasal bacterial flora be predicted from clinical findings? *Pediatrics* 1972;49:596-599.

57. Wald E, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind, placebo-controlled trial. *Pediatrics* 1986;77:795-800.

58. Williams JJ, Aguilar C, Makela M, Cornell J, Holleman D, Chiquette E, et al. Antibiotics for acute maxillary sinusitis. *The Cochrane Library* 2000(2).

59. Paradise JL, Rockette HE, Colborn DK, Bernard BS, Smith CG, Kurs-Lasky M, et al. Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics* 1997;99(3):318-33.

60. Bluestone CD, Klein JO. *Otitis media in infants and children*. Philadelphia PA: WB Saunders, 1988.

61. Douglas RG, Jr., Alford BR, Couch RB. Atraumatic nasal biopsy for studies of respiratory virus infection in volunteers. *Antimicrob Agents Chemother* 1968;8:340-3.

62. Froom J, Culpepper L, Grob P, Bartelds A, Bowers P, Bridges-Webb C, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;300:582-6.

63. Glasziou PP, Hayem M, Del Mar CB. Antibiotics for acute otitis media in children. *The Cochrane Library* 2000(2).

64. Froom J, Culpepper L, Jacobs M, DeMelker RA, Green LA, van Buchem L, et al. Antimicrobials for acute otitis media? A review from the International Primary Care Network. *BMJ* 1997;315:98-102.

65. Rosenfeld RM, Vertrees JE, Carr J, Cipolle RJ, Uden DL, Giebink GS, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty three randomized trials. *J pediatr* 1994;124:355-367.

66. Van Buchem FL, Peeters MF, Van 't Hof MA. Acute otitis media: a new treatment strategy. *BMJ* 1985;290:1033-37.

67. Grenier B. Decision-making in otitis media in children, part 1: epidemiologic data and definitions for a reliable cost-effectiveness analysis. *Clin Microbiol Infect* 1997;3(Suppl):S62-8.

68. Stool SE, Berg AO, Berman S. Otitis media with effusion in young children. Clinical practice guideline. Agency for Health Care Policy and Research, 1994.

69. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. *JAMA* 1993;270:1344-1351.

70. Rosenfeld RM. What to expect from medical treatment of otitis media. *Pediatr Infect Dis J* 1995;14:731-738.

71. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Otitis media-principles of judicious use of antimicrobial agents. *Pediatrics* 1998;101:165-171.

72. Schwartz B, Marcy SM, Phillips WR, Gerber MA, Dowell SF. Pharyngitis-principles of judicious use of antimicrobial agents. *Pediatrics* 1198;101:171-174.

73. Putto A. Febrile exudative tonsillitis: viral or streptococcal? *Pediatrics* 1987;80:6-12.

74. Del Mar C, Glasziou PP, Spinks A. Antibiotics for sore throat (Cochrane Review). *The Cochrane Library* 2000(2).

75. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomized trial of prescribing stratregies in managing sore throat. *BMJ* 1997;314:722-7.

76. Alpert JJ, Pickering MR, Warren RJ. Failure to isolate streptococci from children under the age of 3 years with exudative tonsillitis. *Pediatrics* 1966;38:663-666.

77. Monto A, Cavallaro J. The Tecumseh study of respiratory illness. 11. Patterns of occurrence of infection with respiratory pathogens. *Am J Epidemiol* 1971;94:280-289.

78. Mainous A, Zoorob R, Hueston W. Current management of acute bronchitis in ambulatory care: the use of antibiotics and bronchodilators. *Arch Fam Med* 1996;5:79-83.

79. Vinson DC, Lutz LJ. The effect of parental expectations on treatment of children with a cough: a report from ASPN. *J Fam Pract* 1993;37:23-27.

80. DeLozier J, Gagnon R. *National Ambulatory Care Survey*, 1989. Hyattsville: National Centre for Health Statistics, 1989.

81. Meza R, Bridges-Webb C, Sayer G, Miles D, Traynor V, Neary S. The management of acute bronchitis in general practice: results from the Australian morbidity and treatment survey, 1990-1991. *Aust Fam Physician* 1994;23(8):1550-1553.

82. Orr PH, Scherer K, Macdonald A, Moffatt MEK. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. *J Fam Pract* 1993;36:507-512.

83. Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1996;316:906-910.

84. Becker L, Glazier R, McIsaac W, Smucny J. Antibiotics for acute bronchitis (Cochrane Review). *The Cochrane Library* 2000(2).

85. Gordon M, Lovell S, Dugdale A. The value of antibiotics in minor respiratory illness in children. *Med J Aust* 1974;1:304-306.

86. Taylor B, Abbott G, Mckerr M, Fergusson D. Amoxycillin and cotrimoxazole in presumed viral respiratory infections of childhood: placebo-controlled trial. *BMJ* 1977;2:552-554.

87. Swartz MN. Use of antimicrobial agents and drug resistance. *N Engl J Med* 1997;337:491-2.

88. Little PS, Williamson I. Are antibiotics appropriate for sore throats? Cost outweigh the benefits. *BMJ* 1994;309:1010-1012.

89. Seppala H, Nissinen A, Jarvinen H, Huovinen S, Henriksson T, Herva E, et al. Resistance to erythromycin in group A streptococci. *N Engl J Med* 1992;326(5):292-7.

90. Eliasson I, Holst E, Molstad S, Kamme C. Emergence and persistence of beta-lactamase-producing bacteria in the upper respiratory tract in children treated with beta-lactam antibiotics. *Am J Med* 1990;88(5A):51S-55S.

91. Kunin C. Problems in antibiotic usage. In: Mandel G, Douglas RJ, Bennett J, editors. *Principles and practice in infectious diseases*. 3rd ed. New York: NY: Churchill Livingstone Inc, 1990:427-434.

92. Levy S. *The antibiotic paradox: how miracle drugs are destroying the miracle*. New York: Plenum Press, 1992.

93. Datta N, Faiers MC, Reeves DS, Brumfitt W, Orskov F, Orskov I. R Factors in Escherichia coli in faeces after oral chemotherapy in general practice. *Lancet* 1971;1(7694):312-5.

94. Levy SB. Microbial resistance to antibiotics. An evolving and persistent problem. *Lancet* 1982;2(8289):83-8.

95. Butler JC, Hofmann J, Cetron MS, Elliot JA, Facklam RR, Breiman RF. The continued emergence of drug-resistant Streptococcus pneumoniae in the United States: an update from the Centers for Disease Control and Preventions Pneumococcal Sentinel Surveillance System. *J Infect Dis* 1996;174:986-93.

96. Hammond ML, Norriss MS. Antibiotic resistance among respiratory pathogens in preschool children. *Med J Aust* 1995;163:239-242.

97. Breiman RF, Butler JC, Tenover FC, Elliott JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831-1835.

98. Heffernan R, Henning K, Labowitz A, Hjelte A, Layton M. Laboratory survey of drug-resistant Streptococcus pneumoniae in New York City, 1993-1995. *Emerging Infectious Diseases* 1998;4:113-116.

99. Istre GR, Tarpay M, Anderson M, Pryor A, Welch D, Group TPS. Invasive disease due to Streptococcus pneumoniae in an area with a high rate of relative penicillin resistance. *J Infect Dis* 1987;156(5):732-735.

100. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliott JA, et al. The prevalence of drug-resistant Streptococcus pneumoniae in Atlanta. *N Engl J Med* 1995;333:481-486.

101. Haglund LA, Istre GR, Pickett DA, Welch DF, Fine DP, Group TPS. Invasive pneumococcal disease in Central Oklahoma: emergence of high-level penicillin resistance and multiple antibiotic resistance. *J Infect Dis* 1993;168:1532-6.

102. Collignon PJ, Bell J, Hufton IW, Mitchell D. Meningitis caused by a penicillin and chloramphenicol resistant Streptococcus pneumoniae. *Med J Aust* 1988;149:497-498.

103. Hansman D, Bullen MM. A resistant pneumococcus. *Lancet* 1967;2:264-265.

104. Klugman KP, Koornhof HJ. Drug resistance patterns and serogroups or serotypes of pneumococcal isolates from cerebrospinal fluid or blood, 1979-1986. *J Infect Dis* 1988;158(5):956-64.

105. Klugman KP. Pneumococcal resistance to antibiotics. *Clin Microbiol Rev* 1990;3:171-196.

106. Grimwood K, Collignon PJ, Currie BJ, Ferson MJ, Gilbert GL, Hogg GG, et al. Antibiotic management of pneumococcal infections in an era of increased resistance. *J Paediatr Child Health* 1997;33(4):287-95.

107. Gray BM, Converse GMd, Dillon HC, Jr. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. *J Infect Dis* 1980;142(6):923-933.

108. Jacobs MR, Koornhof HJ, Robins-Browne RM, Stevenson CM, Vermaak ZA, Freiman I, et al. Emergence of multiply resistant pneumococci. *N Engl J Med* 1978;299:735-740.

109. Radetsky MS, Istre GR, Johansen TL, Parmelee SW, Lauer BA, Wiesenthal AM, et al. Multiply resistant pneumococcus causing meningitis: its epidemiology within a day-care centre. *Lancet* 1981;October 10:771-773.

110. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scand J Infect Dis* 1994;26(4):446-52.

111. Gratten M, Naraqi S, Hansman D. High prevalence of penicillin-insensitive pneumococci in Port Moresby, Papua New Guinea. *Lancet* 1980;11:192-195.

112. Clavo-Sanchez AJ, Giron-Gonzalez JA, Lopez-Prieto D, Canueto-Quintero J, Vergara-Campos A, Marin-Casanova P, et al. Multivariate analysis of risk factors for infection due to penicillin-resistant and multidrug-resistant Streptococcus pneumoniae: a multicenter study. *Clin Infect Dis* 1997;24:1052-9.

113. Robins-Browne RM, Kharsany ABM, Koornhof HJ. Antibiotic-resistant pneumococci in hospitalized children. *J Hyg* 1984;93:9-16.

114. Henderson FW, Gilligan PH, Wait K, Goff DA. Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care. *J Infect Dis* 1988;157:256-63.

115. Klugman KP, Koornhof HJ, Kuhnle V. Clinical and nasopharyngeal isolates of unusual multiply resistant pneumococci. *Am J Dis Child* 1986;140(11):1186-90.

116. Klugman KP, Koornhof HJ, Wasas A, Storey K, Gilbertson I. Carriage of penicillin resistant pneumococci. *Arch Dis Child* 1986;61(4):377-81.

117. Levy SB. The challenge of antibiotic resistance. *Scientific American* 1998:46-53.

118. Cohen D, Creech G, Sayers R. Haemophilus influenzae infections in American children living in the U.K. [letter]. *Lancet* 1982;1(8263):101.

119. Soares S, Kristinsson KG, Musser JM, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B Streptococcus pneumoniae from Spain to Iceland in the late 1980s. *J Infect Dis* 1993;168(1):158-63.

120. Munoz R, Coffey TJ, Daniels M, Dowson CG, Laible G, Casal J, et al. Intercontinental spread of a multiresistant clone of serotype 23F Streptococcus pneumoniae. *J Infect Dis* 1991;164:302-6.

121. McGowen J. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis* 1983;5:1033-1048.

122. Baquero F, Martinez-Beltran J, Loza E. A review of antibiotic resistance patterns of Streptococcus pneumoniae in Europe. *J Antimicrob Chemother* 1991;28, Suppl. C:31-38.

123. Jackson MA, Shelton S, Nelson JD, McCracken GH, Jr. Relatively penicillin-resistant pneumococcal infections in pediatric patients. *Pediatr Infect Dis* 1984;3(2):129-32.

124. Pallares R, Gudiol F, Linares J, Ariza J, Rufi G, Murgui L, et al. Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. *N Engl J Med* 1987;317:18-22.

125. Amitai Y, Rotenberg M, Wirtschafter D, Haas H, Michel J. Increasing frequency of penicillin-resistant pneumococci: epidemiological aspects and case-control study. *Isr J Med Sci* 1985;21(4):340-5.

126. Tan TQ, Mason EO, Kaplan SL. Penicillin resistant systematic Pneumococcal infections in children: A retrospective case-control study. *Pediatrics* 1993;92:761-767.

127. Deeks SL, Palacio R, Ruvinsky R, Kertesz DA, Hortal M, Rossi A, et al. Risk factors and course of illness among children with invasive penicillin-resistant Streptococcus pneumoniae. The Streptococcus pneumoniae Working Group. *Pediatrics* 1999;103(2):409-13.

128. Ford KL, Mason EO, Jr., Kaplan SL, Lamberth LB, Tillman J. Factors associated with middle ear isolates of Streptococcus pneumoniae resistant to penicillin in a children's hospital. *J Pediatr* 1991;119(6):941-4.

129. Melander E, Molstad S, Persson K, Hansson HB, Soderstrom M, Ekdahl K. Previous antibiotic consumption and other risk factors for carriage of penicillin-resistant Streptococcus pneumoniae in children. *Eur J Clin Microbiol Infect Dis* 1998;17:834-838.

130. Hansman D, Glasgow H, Sturt J, Devitt L, Douglas R. Increased resistance to penicillin of pneumococci isolated from man. *N Engl J Med* 1971;284(4):175-177.

131. Hansman D, Devitt L, Miles H, Riley I. Pneumococci relatively insensitive to penicillin in Australia and New Guinea. *Med J Aust* 1974;2:353-56.

132. Naraqi S, Kirkpatrick GP, Kabins S. Relapsing pneumococcal meningitis: Isolation of an organism with decreased susceptibility to penicillin G. *J Pediatr* 1974;85:671-673.

133. Appelbaum PC. World-wide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 1987;6(4):367-77.

134. Dixon JMS. Pneumococcus resistant to erythromycin and lincomycin. *Lancet* 1967;1:573.

135. Kislak JW. Type 6 pneumococcus resistant to erythromycin and lincomycin. *N Engl J Med* 1967;276:852.

136. Klugman KP, Koornhof HJ, Kuhnle V, Miller SD, Ginsburg PJ, Mauff AC. Meningitis and pneumonia due to novel multiply resistant pneumococci. *BMJ* 1986;292:730.

137. Howe JG, Wilson TS. Co-trimoxazole-resistant pneumococci. *Lancet* 1972;2(7769):184-5.

138. Markman M, Mannisi J, Dick JD, Filburn B, Santos GW, Saral R. Sulfamethoxazole-trimethoprim-resistant pneumococcal sepsis. *JAMA* 1982;248(22):3011-2.

139. Moore EP, Williams EW. Hospital transmission of multiply antibiotic-resistant Streptococcus pneumoniae [letter]. *J Infect* 1988;16(2):199-200.

140. Hansman D, Mooris S. Pneumococcal carriage amongst children in Adelaide, South Australia. *Epidemiol. Infect* 1988;101:411-417.

141. Evans W, Hansman D. Tetracycline-resistant pneumococcus. *Lancet* 1963;i:451.

142. Turner G. Tetracycline-resistant pneumococci in a general hospital. *Lancet* 1963;ii:1292-1295.

143. Howard AJ, Hince CJ, Williams JD. Antibiotic resistance in Streptococcus pneumoniae and Haemophilus influenzae. Report of a study group on bacterial resistance. *BMJ* 1978;1(6128):1657-60.

144. Cybulska J, Jeljaszewicz J, Lund E, Munksgaard A. Prevalence of types of Diplococcus pneumoniae and their susceptibility to 30 antibiotics. *Chemotherapy* 1970;15(5):304-16.

145. Garau J, Linares J, Dominguez C. Chloramphenicol-resistant pneumococci [letter]. *Lancet* 1981;2(8238):147-8.

146. Meers PD, Matthews RB. Multiply resistant pneumococcus [letter]. *Lancet* 1978;2(8082):219.

147. Levy SB. Confronting multidrug resistance. A role for each of us. *JAMA* 1993;269(14):1840-2.

148. Phelps CE. Bug/drug resistance. Sometimes less is more. *Med Care* 1989;27(2):194-203.

149. Holmberg SD, Solomon SL, Blake PA. Health and economic impacts of antimicrobial resistance. *Rev Infect Dis* 1987;9(6):1065-78.

150. Bradley CP. Uncomfortable prescribing decision: a critical incident study. *BMJ* 1992;304:294-296.

151. Weiss MC, Fitzpatrick R, Scott DK, Goldcre MJ. Pressures on the general practitioner and decisions to prescribe. *Family practice* 1996;13:432-438.

152. Baker R. Development of a questionnaire to assess patient's satisfaction with consultations in general practice. *Br J Gen Pract* 1990;40:487-490.

153. Loda FA, Glezen P, Jr WAC. Respiratory disease in group day care. *Pediatrics* 1972;49(No.3):428-437.

154. Roberts LA. Infection control measures reduce diarrhoeal and acute respiratory infections in child care. A randomised controlled trial [PhD]. The Australian National University, 1998.

155. Samet JM, Lambert WE, Skipper BJ, Cushing AH, Hunt WC, Young SA, et al. Nitrogen Dioxide and respiratory illnesses in infants. *Am Rev Respir Dis* 1993;148:1258-1265.

156. Kleinbaum DG. *Logistic Regression*. 4th ed, 1996.

157. Young G, Spencer J. General practitioners' views about the need for a stress support service. *Fam Pract* 1996;13(6):517-21.

158. Dickinson JA. "The Elsewhere bias". *Med J Aust* 1996;164(7):438-40.

159. ABS. Australian social trends, 1998.

160. Wilson EJ, Nasrin D, Banwell C, Broom D, Douglas RM. Realities of practice. Engaging parents and GPs in developing clinical practice guidelines. *Aust Fam Physician* 2000;29(5):498-503.

161. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing. 5th informational supplement. Document M100-S5. Villanova PN. 1994.

162. Roberts L, Smith W, Jorm L, Ph DB, Patel M, Douglas RM, et al. Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. *Pediatrics* 2000;105(4 Pt 1):738-42.

163. Kotch JB, Weigle KA, Weber DJ, Clifford RM, Harms TO, Loda FA, et al. Evaluation of an hygienic intervention in child day-care centers. *Pediatrics* 1994;94(6 Pt 2):991-4.

164. Collet JP, Burtin P, Gillet J, Bossard N, Ducruet T, Durr F. Risk of infectious diseases in children attending different types of day-care setting. Epicreche Research Group. *Respiration* 1994;61(Suppl 1):16-9.

165. Schwartz B. Preventing the spread of antimicrobial resistance among bacterial respiratory pathogens in industrialized countries: the case for judicious antimicrobial use. *Clin Infect Dis* 1999;28:211-213.

166. Hennekens CH, Buring JE. *Epidemiology in medicine*. first ed, 1987.

167. Graham NMH. The epidemiology of acute respiratory infections in children and adults: a global perspective. *Epidemiologic reviews* 1990;12:149-178.

168. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;315:350-352.

169. Appelbaum PC. Antimicrobial resistance in Streptococcus pneumoniae: an overview. *Clin Infect Dis* 1992;15(1):77-83.

Appendices

Appendix 3

ARIC

Consent Form for Doctors Participating in the ARIC Study

I understand that this is an experimental study designed to test the utility and effectiveness of best practice guidelines in the care of childhood respiratory infections.

I understand that the experiment will involve two groups of general practitioners, for whom a random process will determine whether I am assigned to the early or late intervention group.

I understand that this study will involve me in agreeing to the recruitment of fifteen of my child patients under two years of age, to participate in the study, and that it may require my participation in a series of meetings with the principal investigators and colleagues to help in the forming of the guidelines and to monitor the progress of the study.

I understand that the children who will be recruited from my practice will need to obtain nasal swabs three times in a year for this study.

I understand that my time commitment to the study will be renumerated on a notional basis.

I understand that the information collected as part of this study will be separated from information which identifies me; that I and my patients will be referred to by a code number, and that the code register will be kept separately from the main data base.

The purpose of this study have been explained to me and I support the broad objectives which include a better understanding of patient and doctor expectations and experiences in the care of childhood respiratory infections; a better understanding of

resources currently used in the clinical care of these infections; the development of best practice guidelines; the utility of these guidelines and the effects of the availability of the Cochrane data base of systematic reviews to clinicians.

I have read the information sheet to be provided to patients, and I am agreeing to participate in this study along the lines of the information sheet.

Signed: _____ Date: _____

Witness: _____

ARIC

GP Questionnaire

Acute Respiratory Infection Study

GP number: _____

There are four parts to this questionnaire:

Part A general identifying information is asked. This contact information will be stored separately to ensure your confidentiality and all information submitted on this questionnaire will be stored using a coded number.

Part B asks some questions about your medical practice and associations.

Part C asks about your usual clinical practice in treating acute respiratory infections (ARI) in young children.

Part D enquires about your experiences and attitudes of clinical practice guidelines.

A) General Information

1. Name: _____
2. Practice Address: _____

_____

_____

3. Phone number: _____

4. Fax number: _____

5. E-mail: _____

6. Year of graduation from medical school _____

7. Years of practicing as a GP _____

8. M ☐ F ☐

B) Medical Practice and Associations

1. How many doctors are in your practice?

   ☐ solo ☐ 2-3 GPs ☐ 4 or more GPs

2. How many hours in the surgery do you work per week?

   please specify _____

3. Are you vocationally registered?

   ☐ Yes ☐ No

4. Are you a member of any of the following medical associations?

   ☐ ACT Division of General Practice

   ☐ RACGP

   ☐ AMA

   ☐ Other (*please specify*) _____

5. As a member of the above medical associations, how would you describe your involvement?

	Very Active	**Somewhat Active**	**Occasional Input**	**Member only**	**Not Applicable**
ACT Division	☐	☐	☐	☐	☐
RACGP	☐	☐	☐	☐	☐
AMA	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

6. As a factor in modifying your clinical care of patients, please rank the following in order of importance to you. (1 most important, 7 least important)

- ☐ Journal articles
- ☐ Continuing medical education
- ☐ Medical Textbooks
- ☐ Pharmaceutical Company Representatives
- ☐ Discussions with Colleagues
- ☐ Unsatisfactory outcome of previous treatment
- ☐ Other, *please specify* _____

7. How many hours per week would you spend reading background material about patient care?

please specify _____

C) Clinical Practice

(I) Listed below are hypothetical case profiles of children under two years of age. Please indicate when you would be likely to prescribe antibiotic?

	Very rarely	Rarely	Sometimes	Usually	Often
1. Two year old boy with history of low grade fever and harsh cough for 2 days. On examination, he is irritable, with a normal respiratory rate, clear lungs.	☐	☐	☐	☐	☐
2. Persistant cough for 5 days, afebrile, history of wheezing for the first time, nothing else. On examination, ronchi are present.	☐	☐	☐	☐	☐
3. Cough for one week, thick green nasal discharge. Examination reveals no abnormal finding.	☐	☐	☐	☐	☐
4. Very prone to colds and gets wheezy. This time watery discharge from nose, dry cough, but no fever. Examination reveales no abnormal finding.	☐	☐	☐	☐	☐

5. In children, how often do you diagnose Streptococcal tonsillitis on the basis of history and clinical findings alone?	☐	☐	☐	☐	☐
6. How often do you start antibiotic for a child with pharyngitis pending results of a throat culture?	☐	☐	☐	☐	☐
7. A six month old baby with fever, cough and pulling at right ear. On examination the tympanic membrane is congested and retracted, with limited mobility. No air/fluid level is visible.	☐	☐	☐	☐	☐
8. Two year old child is not taking food for 2 days due to discomfort on swallowing and fever. Examination shows congested tonsils and pharynx, no pus.	☐	☐	☐	☐	☐
9. One year old baby developed fever three days ago, does not eat or play as usual. On examination, fast breathing and wheezing present, but no chest indrawing.	☐	☐	☐	☐	☐

10. Two month old baby is very sleepy since yesterday, not able to drink. On examination fast breathing and chest indrawing with wheezing present. ☐ ☐ ☐ ☐ ☐

11. How often do you prescribe antibiotic treatment for a child with a nonspecific upper respiratory infections (excluding acute otitis media, streptococcal pheryngitis, and sinusitis)? ☐ ☐ ☐ ☐ ☐

(II) **The following statements are about your experience in treating ARI in young children, under two years of age. Please take the time to think about the patients that you have seen over the last two weeks and respond to the followings.**

	<10%	10-24%	25-49%	50-75%	75%
1. Proportion of cases in which you feel parents should have consulted you earlier.	☐	☐	☐	☐	☐
2. Proportion of cases in which you think parents have consulted you earlier than necessary.	☐	☐	☐	☐	☐
3. Percentage of cases which only require symptomatic treatment.	☐	☐	☐	☐	☐
4. Percentage of cases in which you prescribed antibiotics.	☐	☐	☐	☐	☐
5. Percentage of cases admitted to hospital.	☐	☐	☐	☐	☐
6. Percentage of cases where	☐	☐	☐	☐	☐

consultation were unnecessary.

(III) **Please indicate your opinion whether you agree or disagree or not sure about the following statements.**

	Strongly agree	Agree	Not sure	Disagre	Strongly disagree
1. Parents can distinguish those infections that require medical attention from those that don't.	☐	☐	☐	☐	☐
2. Parents want an explanation of their child's illness.	☐	☐	☐	☐	☐
3. You need to explain the difference between viral and bacterial respiratory infections in terms of signs and symptoms and effective treatment.	☐	☐	☐	☐	☐
4. Parents understand the difference between viral and bacterial respiratory infections.	☐	☐	☐	☐	☐
5. Parents understand the role of antibiotics.	☐	☐	☐	☐	☐
6. Parents expect antibiotics when they consult a doctor.	☐	☐	☐	☐	☐

7. Your prerscribing practices would be different if parents did not pressure you for antibiotics. ☐ ☐ ☐ ☐ ☐

8. In your practice, you could decrease the rate of antibiotic prescribing in ARIs without compromising patient care. ☐ ☐ ☐ ☐ ☐

9. Parents are satisfied with reassurance and advice regarding symptomatic treatment for viral infections. ☐ ☐ ☐ ☐ ☐

10. Parent's expectations affect your management decision. ☐ ☐ ☐ ☐ ☐

11. As a way of providing parental satisfaction, you prescribe antibiotics, though it is not indicated. ☐ ☐ ☐ ☐ ☐

12. Parents are satisfied with the information that they receive regarding their children's illnesses. ☐ ☐ ☐ ☐ ☐

13. Antibiotic use is a major factor contributing to the spread of antibiotic resistance ☐ ☐ ☐ ☐ ☐

14. Most parents expect to receive an antibiotic prescription for their child with a nonspecific URI. ☐ ☐ ☐ ☐ ☐

(IV). What are the factors other than the physical findings, that influence you in antibiotic prescribing?

	Strongly agree	Agree	Not sure	Disagree	Strongly disagree
Child's irritability.	☐	☐	☐	☐	☐
Parent's expectation	☐	☐	☐	☐	☐
Previous experience with this patient	☐	☐	☐	☐	☐
The question of litigation	☐	☐	☐	☐	☐
Day care center attendance	☐	☐	☐	☐	☐
Both parents work	☐	☐	☐	☐	☐
History of asthma in the family	☐	☐	☐	☐	☐

D) Clinical Practice Guidelines

1. The following statements are about clinical practice guidelines (**CPGs**). Please tick the response that best reflects your view.

	strongly agree	**agree**	**not sure**	**disagree**	**strongly disagree**
a) CGPs are a useful tool in assisting with patient care.	☐	☐	☐	☐	☐
b) CPGs guidelines are often ambiguous and difficult to interpret.	☐	☐	☐	☐	☐
c) CPGs can improve the quality of health care.	☐	☐	☐	☐	☐
d) CPGs are inflexible and do not allow for the management of each patient's unique condition.	☐	☐	☐	☐	☐
e) Use of CPGs will increase health care cost.	☐	☐	☐	☐	☐

f) CPGs are produced by

organizations that do not understand the needs of the local clinician.	☐	☐	☐	☐	☐
g) CPGs should be produced only for complicated and ambiguous clinical conditions.	☐	☐	☐	☐	☐
h) If CPGs are going to work, general practitioners must be involved in their development.	☐	☐	☐	☐	☐
i) CPGs stifle clinical freedom and innovation.	☐	☐	☐	☐	☐
j) CPGs are a convenient and quick source of information.	☐	☐	☐	☐	☐
k) CPGs can be used in medical litigation.	☐	☐	☐	☐	☐

	strongly agree	agree	not sure	disagree	strongly disagree
l) CPGs are effective in changing clinical practice.	☐	☐	☐	☐	☐
m) CPGs represent the most up-to-date and scientifically sound evidence on clinical care.	☐	☐	☐	☐	☐
n) CPGs developed by clinicians and speciality groups are more medically sound than those developed by government agencies or health insurers.	☐	☐	☐	☐	☐
o) There is too widespread a development of CPGs.	☐	☐	☐	☐	☐
p) CPGs are a bureaucratic imposition.	☐	☐	☐	☐	☐
q) CPGs can be used to improve doctor-patient communication and informed decisions.	☐	☐	☐	☐	☐

r) CPGs will be used as a quality assurance tool in medical audits. ☐ ☐ ☐ ☐ ☐

s) Input from consumers should be sought when developing CPGs. ☐ ☐ ☐ ☐ ☐

3. Have you used clinical guidelines in your practice?

☐ Yes ☐ No

4. If yes, what clinical guidelines have you used?

please specify _____

_____

_____

Thank you for your time answering this questionnaire.

ARIC

Recruiting Information

ARIC study

To receptionists who prepare case notes for Dr._____:

Dr._____ has agreed to participate in a study of general practice care of acute respiratory infections in children. As part of the office staff you will be an integral part of this study and we would greatly appreciate your help in getting this study off the ground. The purpose of this study is to test a new approach to the development of clinical guidelines which will involve the GPs, as well as parents of young children. The study will take the form of a two year randomised trial in which two groups of 30 GPs, randomly assigned, will participate at different times in developing new approaches to care. Parents of a group of young children who are being looked after by the GPs will maintain diaries of their child's respiratory experience, including details of care received from the GP.

The project is funded by the General Practice Evaluation Program, from the Department of Health and Family Services and is being sponsored jointly by the ACT Division of General Practice, the ACT Faculty of the RACGP, and the National Centre for Epidemiology and Population Health. The Director of the project is Professor Bob Douglas who is assisted by two PhD students, Dr Dilruba Nasrin and Ms Eileen Wilson and other research assistants.

We need your help in recruiting patients for this study. Each GP in this study is being asked to recruit fifteen of his/her patients under the age of two years. From

now until the fifteen patients are recruited (one to two weeks), we are asking you to flag the records of any patient under the age of two years who has an appointment with Dr. . Could your please flag the potential study patients by attaching the following documents to the patient record:

1. Recruitment Sheet
2. Parent Information Sheet

When the child and parent are finished seeing the doctor, they will return the recruitment sheet to you. If the parent has agreed to talk to us about the study, could you please fill in the name of the parent and child and their phone number during business hours at the bottom of the recruitment sheet. If the doctor has determined that the patient is not suitable for the study, please do not fill in any personal details. We would appreciate all the recruitment sheets (even those that are not participating in the study) to be returned to the study group, every day or two, preferably by Fax or, if not available, posted to the following address:

Fax: 6249 0740

Dr Dilruba Nasrin/ Ms Eileen Wilson

NCEPH

ANU

Canberra ACT 0200

Throughout the study, the patients will also be having a total of six nasal swabs done. We will be asking for your help in procuring these nasal swabs and will be in touch later in the study to go over the necessary procedures.

If there are any questions about these recruitment procedures, please ring Nasrin or Eileen at **6249 3011**.

Thank you for your help and co-operation

ARIC

Recruitment Sheet

ARIC Study

Patient's Age (months) _____ **Gender** ☐ **M** ☐ **F**

This patient is **NOT** a suitable candidate for this study because:

- ☐ the patient is not a regular patient of mine
- ☐ the patient is unlikely to remain at current residential address for two years
- ☐ the parent is not willing to participate in this study
- ☐ Other (*please specify*) _____

This patient **is** a suitable canidate for the study.

- ☐ The parent(s) of this child has/have agreed to be contacted by the research staff from ANU.
- ☐ I have given the parent the ARIC study information sheet.

Patient's name _____

Parent's name _____

Phone number _____

Form to be returned by Fax to Eileen Wilson or Dilruba Nasrin at: 6249 0740

NCEPH, ANU, Canberra ACT 0200

ARIC

Information on the Study

of

Acute Respiratory Infections in Children

(ARIC)

What is the purpose of this study?

This study hopes to tackle a problem that is a common worry for parents and doctors alike. How do we best manage cough, colds, ear, chest and sinus infections in young children and how do we make sure we are using the available drugs in the best possible way? We hope to clarify what patients and their doctors expect and experience in the care of young children with these respiratory infections. The study will explore new ways of sharing information and knowledge between the doctors, scientists and parents or patients. We will also test some new ways for the setting up of guidelines for good quality care. The study is a trial which involves fifteen children from the practice of each participating doctor. About 60 doctors in Canberra are taking part.

Why do this study?

These respiratory infections are a very common cause of visits to the doctor. They result in the use of very large amounts of antibiotics and other medicines. Scientists around the world are concerned by the fact that antibiotics which can control these organisms which cause infections are no longer working. The organisms are becoming resistant to antibiotics. A great deal of information has become available about what might be called 'best practice' in the care of these infections.

We think it is important that parents of young children are actively involved with their doctors in the care of their children with respiratory infections and that this active involvement will help to determine and define what happens in the future care of children.

This study is in the form of a controlled trial in which we will collect information, not only about what doctors and parents do now in the care of children with these infections, but also test the effects of improving the information that is given to parents and doctors which helps them to make their decisions about the child's care.

Sixty doctors in Canberra who have recruited a total of 900 children will be divided into two equal groups. One group will be involved in this information sharing process early on in the study. The other group will be involved a little later.

What do I have to do?

We are asking parents of all children in the study to keep a diary of the child's medical experiences over a period of two years. To do this we will give you a calendar sheet every month which we would like you to record by jotting down on the calendar we provide, if your child is feeling well or if he/she is showing any signs of illness such as a runny nose or cough. These sheets should be returned every month to our researchers and should not take more than a minute or two every day to complete. The diary should also be filled in when the child visits your doctor. The treatment that your doctor suggests or any home remedies you have given your child should be entered onto the diary. After any visits to the doctor we hope you will take some time to fill in the supplementary form which asks some questions about your visit with the doctor. We also hope that some of the parents will come along to group discussions with the researchers where issues, concerns and experiences about their child's care can be talked about in an open and frank manner.

We will be comparing the information from the records of the 450 children in the early involvement group with the information obtained from the group of 450 children that is involved a bit later. We want to see if improving the access to information makes a difference to the way parents and doctors deal with these infections.

To monitor the effects of any changes in treatment we will ask that your child have a nasal swab three times a year during the two year study. The nasal swab will tell us about any changes in the pattern of antibiotic resistance of an organism named pneumococcus which is carried in the nose of about 30% of normal healthy children.

What are the risks and benefits?

There are no risks involved. Throughout the two years of the study we hope that you will continue to receive most of your child's medical care from the same doctor so that we can keep track of the effects of your doctor's and child's involvement in the study. The relationship you have with your doctor should not change in any way. The study will be looking at your views and your doctors about the way these infections are treated and prevented. The aim of the study is to improve care where parents and doctors agree that improvements are needed.

Who is running the study?

The study is being carried out by a partnership between the National Centre for Epidemiology and Population Health, the ACT Division of General Practice, and the Royal Australian College of General Practitioners Training Program. The chief investigator on the study is Professor Bob Douglas, who is Director of the National Centre, and who has had a lifetime of research in this area, especially in seeking to understand better ways of preventing and treating these common infections in children. The project is funded by the National General Practice Evaluation Program. The team working on the study is in touch with the latest developments in the treatment and prevention of these respiratory infections.

A research worker will telephone you to discuss further your possible involvement in the project, including what you would need to do about keeping the diary.

ARIC

Parental Consent Form

ARIC Study

I have read the information sheet on this study and understand its contents. I understand that participation in the study involves me in maintaining a record of my child's medical experiences over the next two years for purposes of research. I will keep a diary on my child's illnesses and this will be used to monitor progress in the study. I also understand that my child will need to have a nasal swab done six times over the two year study period. I understand the information will be stored, using a code number rather than any information that enables my child or me to be personally identified on the computer database.

I agree to my child's participation in the study on the basis of the information supplied to me about the studies purposes and activities.

Signed: _____ Date: _____

Witness: _____

ARIC

Parent Questionnaire

Acute Respiratory Infections in Children

(ARIC)

ID number _____

This questionnaire will ask questions about the general health of your child and more specific questions about the respiratory health of you and your child. We will also be asking about environmental factors that may affect the respiratory health of your child such as smoking, breastfeeding, childcare and home heating. Finally we will be asking questions about specific respiratory illnesses in your child and your experiences and expectations in the care and treatment of your child during these illnesses.

General Information

The following questions ask some general identifying information. This contact information will be stored separately to ensure your confidentiality and all information submitted on this questionnaire will be stored using a coded number.

1. Parent's name: _____
2. Child's name: _____
3. Home address: _____

   _____

   _____
4. Phone number: (H)_____ (W)_____

The following questions asks some general information about yourself, your child and other family members.

5. Date of birth of child: _____

6. Sex of child: ☐ M ☐ F

7. Number of siblings: _____

8. Ages of siblings: _____

9. Age of mother: _____

10. Age of father: _____

11. Schooling of parents (*please circle highest schooling obtained*)

	Mother	Father
finished primary school	1	1
finished high school.....	2	2
trades or TAFE training	3	3
university graduate	4	4
postgraduate degree	5	5

12. Approximately what is your family taxable income?

☐ <$30,000

☐ $31,000 - $45,000

☐ $46,000 - $60,000

☐ >$60,000

13. In what country were the parents of this child born?

Mother _____

Father _____

The following questions ask about aspects of your child's care and various environmental factors in your home.

14. Was your child breastfed?

☐ Yes ☐ No

15. If yes, for how long?

_____

16. Does your child attend day care?

☐ Yes ☐ No

17. If yes, what kind of day care does your child attend?

☐ In the care of another family member

☐ Private home care

☐ Family Day Care

☐ Day Care Centre

18. How many hours per week does your child attend day care?

☐ <20 hours

☐ 21 - 40 hours

☐ >40 hours

19. Do you, your child's carer or any member of your household smoke?

☐ Yes ☐ No

20. What kind of heating system is in your house?

- ☐ open fire
- ☐ wood stove
- ☐ electric
- ☐ gas, unvented
- ☐ gas, vented

The following questions ask about the general health history of your child.

21. Has your child had any major illness?

☐ Yes ☐ No

22. If yes, what was the nature of this illness?

_____

_____

23. Is your child fully immunized for his/her age?

☐ Yes ☐ No

The following questions ask about events concerning the birth of your child.

24. How many weeks pregnant was the mother when your child was born?

- ☐ <28
- ☐ 28 - 31
- ☐ 32 - 36
- ☐ 37 - 40
- ☐ >40

25. What type of delivery did your child have?

- ☐ vaginal
- ☐ caesarean
- ☐ forceps

26. Did the mother have any respiratory illness in the year before the birth of your child?

☐ Yes ☐ No ☐ Don't remember

27. While the mother was pregnant with your child, did she experience any significant sleep difficulties?

☐ Yes ☐ No ☐ Don't remember

We would like to understand better, how parents deal with a number of common respiratory problems in their children under two years of age. The following are a list of symptoms. Please think of your children in these situations and tell us whether you would take him/her to the doctor always, more than half the time, about half the time, less than half the time or never.

For each symptom, please tick what you would do :

	Always	More than half	About half	Less than half	Never
a. Harsh cough only	☐	☐	☐	☐	☐
b. Fever 38°c for 2 days	☐	☐	☐	☐	☐
c. Fever, cough, Fast breathing	☐	☐	☐	☐	☐
d. Cough with wheeze	☐	☐	☐	☐	☐
e. Restlessness only	☐	☐	☐	☐	☐
f. Runny nose with green discharge	☐	☐	☐	☐	☐
g. Cough with fever	☐	☐	☐	☐	☐
h. Cough with yellow / green sputum	☐	☐	☐	☐	☐
i. Blueness of lips	☐	☐	☐	☐	☐
j. Trouble breathing	☐	☐	☐	☐	☐
k. Sore throat	☐	☐	☐	☐	☐
l. Not eating normally	☐	☐	☐	☐	☐
m. Disturbed sleep for blocked nose	☐	☐	☐	☐	☐
n. Ear pain with no	☐	☐	☐	☐	☐

other symptoms

o. Discharge from ear ☐ ☐ ☐ ☐ ☐

In the following section, some common situations are presented that you may have faced with your child. Following the situation are statements about some ways of handling these situations. Please think about each statement for a moment and then decide whether you strongly agree, agree, disagree or strongly disagree with each statement.

A. Your child developed a runny nose and mild cough last night and today is off his/her food. He/she seems otherwise well, though you think the temperature is slightly raised.

	Strongly agree	Agree	Disagree	Strongly disagree	Not sure
I will just wait and see how the child goes throughout the day.	☐	☐	☐	☐	☐
My child needs to be examined by a doctor.	☐	☐	☐	☐	☐
I will talk to the chemist about what kind of treatment to give my child.	☐	☐	☐	☐	☐
It is very important that my child gets antibiotic to help clear the infection.	☐	☐	☐	☐	☐

B. Your child woke with a harsh croupy cough in the middle of the night. His/her voice sounded like a seal's bark. Breathing was not rapid. He/she was not distressed. But it worried you.

	Strongly agree	Agree	Disagree	Strongly disagree	Not sure
I will watch my child throughout the day.	☐	☐	☐	☐	☐
My child needs to be seen by a doctor.	☐	☐	☐	☐	☐
Antibiotic will improve my child's condition.	☐	☐	☐	☐	☐
My child needs hospital care, as breathing difficulties might develop.	☐	☐	☐	☐	☐
I shall go for some cough medicine.	☐	☐	☐	☐	☐

C. Your child was restless last night and woke this morning with slight wheezy cough. This has never happened to your child before with a cold. What is your idea about this situation?

Slight wheezing is common in respiratory infections.	☐	☐	☐	☐	☐
My child needs to be seen by a doctor.	☐	☐	☐	☐	☐

My child should receive antibiotics.	☐	☐	☐	☐	☐
My child needs to be hospitalised.	☐	☐	☐	☐	☐
My child may need asthma treatment.	☐	☐	☐	☐	☐

D. Your child woke at night crying with what seems to be pain in the ear. He/she was irritable, but settled with panadol. Next morning, he/she is still pulling at the ear. There is no discharge from the ear but temperature is slightly raised.

	Strongly agree	**Agree**	**Disagree**	**Strongly disagree**	**Not sure**
I'd like to continue panadol for few days.	☐	☐	☐	☐	☐
My child needs to be examined by a doctor.	☐	☐	☐	☐	☐
Earache is a natural part of growing up so I won't worry about it.	☐	☐	☐	☐	☐
Ear infections should be treated by antibiotic.	☐	☐	☐	☐	☐
I shall go to the chemist for some ear drops.	☐	☐	☐	☐	☐

E. Your child is complaining of pain in the throat. He/she is miserable and seems to have some enlargement of the glands in the neck. His/ her temperature is raised.

	Strongly agree	Agree	Disagree	Strongly disagree	Not sure
My child needs to be seen by a doctor.	☐	☐	☐	☐	☐
I will wait a day or two to see if it gets better by itself .	☐	☐	☐	☐	☐
I will give the child warm, sweet drink to sip, such as honey and lemon.	☐	☐	☐	☐	☐
Antibiotic is necessary as soon as possible, as complications from sore throat are very common.	☐	☐	☐	☐	☐
I will go to the chemist for some medicine.	☐	☐	☐	☐	☐

F. Please tell me if you agree or disagree with each of the following statements.

	Agree	Disagree	Don't know
Antibiotic will help to cure a cold	☐	☐	☐
Treating a cold with antibiotics will help to prevent an ear infection.	☐	☐	☐
Antibiotics should be stopped as soon as the child feels better.	☐	☐	☐
Some germs are becoming harder to treat with antibiotics.	☐	☐	☐
If antibiotics are overused, they will not work as well for treating infections.	☐	☐	☐
If antibiotics are used frequently to a child, then the child may be infected with bacteria that are hard to treat.	☐	☐	☐

G **Think back to your last visit to your GP for your child's illness. Please read the following statements and tick the response that best reflects your view.**

	Strongly agree	Agree	Disagree	Strongly disagree	Not sure
I was totally satisfied with my visit to the doctor.	☐	☐	☐	☐	☐
The doctor was very careful to check everything when examined my child.	☐	☐	☐	☐	☐
I wished to spend a little longer with the doctor.	☐	☐	☐	☐	☐
I would have liked the doctor to tell me a little more about my child's illness.	☐	☐	☐	☐	☐
The doctor told me everything about the treatment.	☐	☐	☐	☐	☐
The doctor gave me very clear advice about how to care for my child with this illness.	☐	☐	☐	☐	☐
The doctor was interested in my child as a person, and not just his/her illness.	☐	☐	☐	☐	☐

I decided to follow the doctor's advice because I thought he/she was right.	☐	☐	☐	☐	☐
The time I was allowed to spend with the doctor was not long enough to deal with everything I wanted.	☐	☐	☐	☐	☐

Please feel free to make further comments on this topic.

_____

_____

_____

Thank you for filling out the questionnaire.

Diary Information

Every month you will receive a diary and reply paid envelope in the post. Here is your diary for the ARIC study for the next month. We have also included a sample filled-out diary as an example. Each diary covers one month. We suggest you to keep the diary on your fridge and fill it out each night or a similarly convenient time and place. Some months you will also receive a newsletter letting you know the progress of the study.

If your child is well, all you need to do is tick in the right-lower corner of each box.

If he/ she has a cold, then you should put an asterisk (*) in the right-lower corner of the box and indicate which symptoms are present, ie. cough, runny nose, blocked nose, fever, wheezy breathing, etc.

If you are giving your child any medication, or go to doctor or hospital or the child has any other illness, then you need to turn over the sheet and fill out the detail under the specific column like "medication given", "Doctor or hospital visits" etc.

Before you send your diary back in the reply paid envelope provided, you should also answer the question on the back of the diary about breastfeeding for the month.

What the sample diary shows is that, Johnny had a cold from the 5th to 12th August started with runny nose (R), then a dry cough (D). His parents visited the doctor on 8th (on the back of the diary) as he developed wheeze (W) and fever (F). Doctor prescribed panadol, amoxil (antibiotic) and ventolin for him. He took medication from 8th to 12th. But he visited the doctor again on 16 th, as he was pulling the ears since 15th. Doctor examined him and found nothing significant. He had a hospital visit on 29th for a cut on the leg and he needed two stiches for the cut and was adviced to take panadol for pain. Details of medication, doctor and hospital visits are shown on the back of the diary.

Below we have given a list of what we mean by the various terms like dry cough, cough with phlegm, runny nose, blocked nose, fever, wheezy breathing, pulling at ears, sore throat, hoarse voice and discharge from ears.

A carefully completed diary will give us very important information and will be very valuable in our attempt to help GP's and parents to provide better care for children with these acute respiratory infections.

Thank you for helping us in this way.

Please feel free to ring us for any queries.

Nasrin or Eileen

Tel: 6249 3011

Symptom definition:

Dry cough: If the cough is not associated with phlegm. Mark with **D** if your child coughed frequently in the day.

Cough with phlegm: When the cough sounds loose or your child brings up phlegm with the cough. Mark with **C** if your child has this sort of cough.

Runny nose: Discharge of clear liquid from the nose. Mark a **R** on the days this occurs.

Green nasal discharge: Discharge of green or yellow liquid from nose. Mark a **G** if your child has this symptom.

Blocked nose: This refers to your child being unable to breath through the nose and having to breathe through the mouth. Mark a **B** for this symptom.

Fever: If you feel your baby hot. It is better to measure the temperature under the armpit with a thermometer. If it is >37 degrees, it is a fever. Mark a **F** when this occurs.

Wheezing: Whistling sound that comes from the chest during breathing. Breathing may be difficult in this situation. Mark a **W** for this symptom.

Hoarse voice: If the voice is changed and become rough or abnormally deep or harsh. Sometimes the voice is so hoarse that it is difficult to talk. Mark a **V** if your child suffers from this.

Ear pulling / Earache: Sometimes children pull their ear before sleeping. But if your child pulls the ear repeatedly other than sleeping, or if you think your child is experiencing pain in the ear, please mark a **E**.

Discharge from ears: It may be clear or yellow discharge. Mark **P** when this occurs.

Sore throat: If you notice or child complains difficulty in swallowing or pain in the throat. Mark a **T** if this occurs to your child.

NOVEMBER

Name _____ ID # _____
(first) (last)

Sun	*Mon*	*Tue*	*Wed*	*Thu*	*Fri*	*Sat*
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	9	20
21	22	23	24	25	26	27
28	29	30				

Record each symptom your child experiences every day

Mark each day you think your child has a cold with a star

1997

C = cough with phlegm
P = discharge from ears
R = runny nose
B = blocked nose
F = fever (feels hot)
W = wheezy/noisy breathing
T = sore throat/ swallowing difficulty
E = pulling at ears / earache
G = green nasal discharge
D = dry cough
V= hoarse voice

If any of the following happens to your child give more details on the back:

medication given **doctor visit** **hospital visit**

Medication Given

(prescribed or over the counter or home remedy)

Name	Dates given	
	start	end

Type of Feeding this month ***(please tick)***

Was the child breast fed at all this month?

☐ Yes / No ☐

If yes,

☐ Whole month-

☐ To date _____

***Doctor (D) or Hospital (H) visits**

Date	D/H	Study Doctor	Reason

Other Illnesses

Date	Details

Hospital Stays

Dates	Reason

Any Queries about filling in this respiratory diary, please ring **Eileen** or **Nasrin** on **6249 3011**.

Comments or Further Information: _____

_____

_____

ARIC STUDY

Guidelines for Parents

- Children will average about six respiratory infections every year. Children who attend child care centres, are not breastfed, have poor nutrition or are exposed to cigarette smoke can expect to have more respiratory infections.
- The majority of respiratory infections are caused by viruses and will get better by themselves.

* Antibiotics have no effect on viruses.

- Green/yellow nasal discharge is a normal part of a cold, usually occurring 2 - 6 days after the start of a runny nose and often precedes recovery from colds.

* Antibiotics are definitely not needed solely for green/yellow nasal discharge.

- Studies have shown that cough medicines, antihistamines, and decongestants do not offer any real benefit in the treatment of respiratory infections.
- Paracetamol in the right doses, should be used for symptom relief. Humidification or vaporisers, vaporubs, saline nasal drops, vitamin C, honey and lemon drinks, plenty of fluids and bed rest all may help in easing the symptoms of respiratory infections.

* Antibiotics are needed for serious chest infections (rapid breathing or chest indrawing). Most middle ear infections and sore throats do not need antibiotics.

- Antibiotics have no effect on the temporary hearing loss seen after ear infections and only a moderate benefit on pain. In the majority of ear infections, pain lasts for only one day. This pain usually can be treated effectively with proper doses of Paracetamol.
- If you have any concerns about your child's health or any questions about these guidelines, please discuss them with your GP.

Principles Guiding General Practice Management of Respiratory Infections in Children in ARIC Study
Canberra 1998

1. The alarming growth in antibiotic resistance by respiratory bacteria means that antibiotics must be reserved as far as possible for their life-saving potential and for children at risk of serious complications.

2. The vast majority of respiratory infections in children under 4 years of age are self-limiting. Viruses and bacteria are jointly involved in these infections, the most serious and troubling of which are otitis media, sore throats, and pneumonia.

   2a. Each of these three can be followed by life-threatening disease or serious complications which are avoidable through judicious use of antibiotics.

3. The tendency to use antibiotics as a general insurance policy whenever middle ear infection or streptococcal sore throat infection are suspected is now counterbalanced by the knowledge that there are potentially serious consequences from excessive use of these life-saving drugs, both to individuals and the community, and that the benefits in the vast majority of cases are trivial.

4. As a group of general practitioners who have carefully explored the evidence together with experts who have systematically examined this evidence, we have agreed on a conservative course of action with respect to antibiotic prescribing which, nevertheless, recognises that each child must be carefully assessed and managed in their own best interest. Parents need information of a specific nature about what to do to treat specific symptoms and danger signs to alert them to the need for professional assessment.

   We support the use of the ARIC prescription pad and posters and information sheets which will improve parental understanding of the issues and reduce unrealistic expectations of the benefits of these powerful drugs.

5. Where pneumonia is suspected (from the presence of a measured respiratory rate in excess of 40 respirations per minute, chest indrawing, cyanosis, and/or generally ill appearance) antibiotic therapy is certainly desirable.

6. Where infection of the middle ear is suspected, antibiotic treatment is by no means routinely desirable. Antibiotics do little to shorten the duration of pain and apparently nothing to shorten the duration of deafness which accompanies fluid in the middle ear. Careful analgesia with Paracetamol at a therapeutic dose will be more effective in reducing symptoms than antibiotics and, provided there is no mastoid tenderness and the tympanic membrane is not bulging, an expectant approach is justifiable.

7. Purulent exudate on the tonsils or in the pharyngeal area in children under 4 is very often caused by viral infections and not necessarily by group A streptococci. The concern for complications of rheumatic fever and glomerulonephritis has dictated a liberal use of antibiotics for this condition in the past, but a more conservative approach is now justified.

8. We believe that sore throats, even in the presence of pus should not be managed with antibiotics unless there is laboratory evidence that group A haemolytic streptococci are present on the throat swab. That means that in these cases, a throat swab should be collected and the result known to be positive before antibiotic therapy is commenced.

9. Doctors need to evaluate each child with a respiratory illness on its merits and make their therapeutic decisions accordingly. However, they also need to instruct parents in the use of simple harmless treatments. These include:

- hot lemon and honey drinks;
- steam;
- Paracetamol in appropriate dosage;
- Vitamin C;
- (and gentle chest percussion) for a troublesome productive cough.
- Nasal saline drops may help to clean out a blocked nose and
- warmed olive oil may relieve the discomfort of a painful middle ear.
- Antihistamines and cough suppressánts are of little proven usefulness.

Time spent with parents in helping them to understand the natural course of the illness, which afflicts most children about six times a year, is time well spent.

Procedure of nasal swab collection

I employed 2/3 field workers to collect the nasal swabs during each collection. Most of them were working as laboratory scientists at the Canberra Hospital.

Setting: I used two settings for four sets of swab collection.

The first set of swabs were collected from the children from their GPs' surgeries with the anticipation that the parent would feel comfortable to have the procedure done in the GP's surgery. I contacted every GP to see if they would agree to allow us to use the surgery for one hour in the evening period for swab collection. After deciding a date and time with the GP, I sent a letter to each parent informing them the date, time and venue for swabbing. Finally in the night before the swab collection, I rang each parent to remind the date. The research assistants collected swabs for one hour during the evening at three surgeries for three days in a week. During the last week of collection, they collected swabs from the residence of a few children who could not attend the swabbing due to inavailability of transport. I also used Canberra Hospital Pathology Outpatient for one morning to collect swabs from the children who missed their actual date.

From my experience during first swab collection, it was very difficult to arrange for GPs' surgeries for swab collection. Most of the GPs were practising in a group practice where other colleagues might not feel comfortable with the procedure during surgery hours. Therefore I organised health centres and public Libraries for collecting swabs during second to fourth rounds. I made a schedule with all venues with addresses and date and time. About a month before collection started, I sent two copies of schedule to every parent, asking them to select one specific date and venue and to return me one copy but to keep another copy with them as a reminder. I employed a research assistant to help me in reminding parents on the night before the date of swab collection.

Procedure of Swab collection

The child's name, identification number and specimen site (right or left nostril), date and time of collection were recorded on the request form and also on the Stuarts media container and agar plate to identify the individual swab. The cotton tip of the swab stick was moistened by

inserting into the Stuarts media. The parents were asked to gently held the child's head while the swab collector twisted the cotton tip of the swab stick around one nostril. The cotton bud was then spread on the surface of the blood agar plate containing 5 µg/ml of gentamicin, by twisting the swab stick to make a circle of 50 cent size. All the specimens were transported immediately to the Canberra Hospital Microbiology Laboratory. The identification number, date of birth of the children were immediately entered into the computer system of the Pathology Department of the Canberra Hospital.

The ARIC Study Newsletter

National Centre for Epidemiology and Population Health

in cooperation with Royal Australian College of General Practitioners

and the ACT Division of General Practice

MAY 1998

Dear Parents,

Thanks for your active and enthusiastic participation in the ARIC study. We have completed the first stage of the study, the success of which is due to your help and the help of your GPs. Winter is knocking at the door. We hope you are finding the diary-keeping process straightforward and interesting. Diaries and the nasal swabs, are very important parts of the research.

Where are are we now?

Fifty-four Canberra GPs and five hundred and forty children are participating in the study. We are in the late stage of development of some new guidelines for respiratory infections in children which will be tried out first by 24 GPs and their patients in the "early" group..The "later" group will consider use of these guidelines later this year.

How have we developed the guideline?

We have involved GPs and some parents in a series of meetings, where they described their expectations and experiences. We have used this material as well as evidence from the medical literature to develop the trial guidelines.

What is your involvement?

Parents have been enormously helpful by keeping the child's health diary,as well as participating in group meetings. We would appreciate you keeping up this effort in recording and sending

details of health information, including medication and doctor visits, especially during the important Winter season.

What's the nasal swab for?

We have now collected nasal swab from 80% of children in the study. Special thanks to you all for your cooperation. We hope to complete this process in a couple of weeks. In the next newsletter we will provide some data from the swabs. We are working with A/Professor Collignon at the Canberra Hospital to discover the levels of drug resistance of common nasal bacteria. The information is of scientific importance, but the details of sensitivity are not pertinent to clinical care of individual children. So we will provide you the overall level of the resistance. We appreciate your continuing contribution in the process.

Winter!!!

Respiratory infection season is close upon us. We hope you and your children will come through this cough and cold season with minimal problems. We hope to send you another newsletter towards the end of Winter with some data of our preliminary analysis. We wish you a happy Winter.

Contact: The ARIC team

Nasrin or Eileen-62493011

The ARIC Study Newsletter

National Centre for Epidemiology and Population Health

in cooperation with Royal Australian College of General Practitioners

and the ACT Division of General Practice **July 1998**

Dear Parents,

This is to let you know that the ARIC Study is progressing magnificently thanks to the warm cooperation we have received from parents, doctors and the Canberra Hospital. It is also to let you know what we have learnt from the first round of nasal swab tests in the 461 children who had their noses swabbed. As you know, one of the concerns that prompted this research is the growing resistance of common respiratory germs to widely used antibiotic drugs. We are trying to find the best way to deal with common respiratory infections in childhood without fostering the development of resistant bugs.

This first round of swabbing was to get a base-line level in Canberra children of a common organism known as the pneumococcus which tends to be present in the noses and/or throats of all of us from time to time. At any one time up to 30 or 40% of us carry this germ in our noses and mostly they do not cause any problem. Indeed in this study, 37% of the swabs collected grew a pneumococcus which is almost exactly what we expected. The laboratory has carefully tested the level of antibiotic resistance to a number of antibiotics and found, also as we might have predicted, that about half of the bugs were partially "resistant" to one or more of the antibiotics tested. This also conforms to the trend around the world.

The important feature of our study is that we will try to monitor, over time, whether levels of resistance will change in response to differing prescribing actions by doctors and modified treatment actions by parents. That is why your diaries are so important and why we need to continue the study over a total period of two years.

Why pneumococcus is so important?

We are using this bug as our marker because it is an important cause of ear infections, sinus infections, pneumonia and other complications of respiratory infections and because a lot has been learnt in recent years about the mechanisms of its growing resistance to antibiotic drugs. It is quite normal for it to be found incidentally in normal healthy children. Along with other bacteria, this bug is becoming increasingly resistant to a number of our most widely used antibiotics. This is of concern worldwide and our finding of resistance level is consistant with what is happening elsewhere. We need to find effective ways to arrest the growing resistance trend before it does become a serious threat.

What does "resistance" mean?

It means that the bug has partially adapted to antibiotic drugs so that higher and higher doses of antibiotics may be needed to prevent its effects if it starts to proliferate in the ear, in the lung, in the sinuses, or in the blood. There is growing realisation around the world that all of us have become rather excessive in the use of these powerful agents and that we will need to be more cautious about when and where they are used in the future. Our study is about exploring new ways of handling respiratory infections in childhood that could minimise unnecessary antibiotic use.

How bugs become resistant?

Each time we take antibiotics, sensitive bugs are killed, but the resistant bugs are not. They grow and multiply. Frequent and long-term uses of antibiotics are the main causes of development and spread of resistance. Resistant bugs can spread to others in the community, even if people don't take antibiotics.

Is resistance permanent?

The evidence suggests that resistant strains don't necessarily persist. However carriers of resistant bugs can be re-infected which makes the treatment difficult and expensive. The evidence also suggests that we could change the worrying trend of increasing resistance. In this study, we are comparing the level of resistance to the types and extent of antibiotic prescription to which

children in the study have been exposed. We believe this project will throw very important light on the problem that could benefit not only your children but children throughout Australia and elsewhere.

Is the finding on my child's swab relevant to her clinical care?

The findings on individual children are much less important than the findings across the whole study population. The evidence suggests that these bugs transfer rapidly around schools and playgroups anyway and what is most important is the trend across the whole community. That is why we hope you will continue to work with us on this very important project. We will continue to keep you informed on progress as we undertake the analysis of the diaries which are being kept so well by so many Canberra parents. We know that carriage in the nose varies in individuals from week to week and therefore the finding of a resistant bug in an individual child may have no relevance to clinical care. But the findings emphasise the need to monitor the children again at the peak of winter, when children frequently get antibiotics. The schedule for the next round is enclosed with the newsletter. We will appreciate your help to collect nasal swabs in the next round.

Contact: The ARIC team
Nasrin or Eileen-6249 3011

The ARIC Study Newsletter

National Centre for Epidemiology and Population Health

in cooperation with Royal Australian College of General Practitioners and the

ACT Division of General Practice **July 1998**

Dear Colleagues,

We are now ten months into the two-year ARIC study. Respiratory data from your young patients continues to flow in and we are getting some very important results. We believe this project is at the cutting edge of evidence-based health care and has the potential to make an empowering change in general practice.

Where are we with the ARIC study?

The study includes 519 actively involved study children and 53 GPs. Respiratory diaries are consistently coming in and giving us a wealth of important information. During November through April, 23 GPs in the early group and some of the parents of their patients were involved in a series of meetings to develop a set of guidelines for use in managing ARI. This process as well received with very positive and encouraging feedback from our evaluation questionnaires.

Guidelines for parents in the early group have been distributed. GPs in the early group also have the clinical guidelines they have helped to develop together with other supporting materials. We hope these guidelines will prove useful parents and GPs through the winter coughs and colds season.

Early next year the GPs in the later group will be invited to consider the guidelines that the early group has developed. We will be monitoring parent management of ARI and consequent health outcomes over the two winters.

Results of Nasal Swabs

During April, we have collected nasal swabs from 461 of our study children (88%). Pneumococcus was isolated from 172 samples. This isolation rate of 37.3% is comparable to or better than other studies. We tested these isolates for resistant levels to seven commonly prescribed antibiotics. Half of the isolates were resistant to one or more of the antibiotics. 23.3% of these isolates were resistant to two or more antibiotics. 1.2% of the pneumococcus isolates were resistant to all of the antibiotics tested, except cefotaxime to which none of the isolates were resistant.

We will be starting the next round of nasal swabs at the end of August. We plan to do this swabbing at community health centres and The Canberra Hospital. We hope this change of venue will be more efficient and reduce the burden on individual surgeries.

If you have any questions about the study, please do not hesitate to ring us at the following number.

Contact: The ARIC team
Nasrin or Eileen-62493011

The ARIC Study Newsletter

National Centre for Epidemiology and Population Health

in cooperation with Royal Australian College of General Practitioners

and the ACT Division of General Practice **September1998**

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We will be starting the next round of nasal swabs at the end of August. We plan to do this swabbing at community health centres and The Canberra Hospital. We hope this change of venue will be more efficient and reduce the burden on individual surgeries.

ARI Update

I recently attended the WONCA Conference (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) in Dublin, and participated in a number of meetings that were discussing some of the issues we have been discussing in this project. Dutch antibiotic prescribing rates for respiratory infections ar4e considerably lower than those in Australia. So is their incidence of antibiotic resistance. It is conforting to know that every country in the world is facing our dilemmas.

In particular, the issue of what to do about possible streptococcal throats is exercising GPs everywhere. I am satisfied that the consensus we reached in the discussions I March and April is as practical and defensible as any other course of action being proposed elsewhere. That is, sore throats, even in the presence of pus, should not be managed with antibiotics unless there is laboratory evidence that group A Haemolytic streptococci are present on the thraoat swab. That means that in these cases, a throat swab should be considered and the results known to be positive before antibiotic therapy is commenced.

On the issue of otitis media also, there is very variable prescribing around the world. Once again, I think our consensus in Canberra is absolutely defensible. That is, careful analgesia at a therapeutic dose will be more effective in reducing symptoms than antibiotics and, provided there is no mastoid tenderness and the child does not look seriously ill, an expectant approach is justifiable and should be discussed with the parent.

I look forward to hearing from you on your experience in implementing the guidelines later in the year. We have recently sent out a Newsletter to parents of children in the early group, reinforcing the messages contained in the guidelines that was distributed to them in May.

It was clear to me at the Dublin meeting that the study w are doing here is at the international cutting edge of this work.

Looking forward to your continuing support.

RM Douglas

for the ARIC Team

If you have any questions about the study, please do not hesitate to ring us at the following number.

Contact: The ARIC team

Nasrin or Eileen-62493011

Happy Birthday Christian

Appendix 6

Appendix 6.1

To see the association between any beta lactam use during different periods before swab collection and isolation of penicillin resistant pneumococci after adjusting for repeated swabs fromt he same child.

Table: Effect of any beta lactam use during each two monthly period on penicillin resistance, adjusting for the cluster effect of a child

Time before swab collection (months)	Total isolate	OR	P value	Lower 95% CI	Upper 95% CI
0-2	522	2.03	0.01	1.15	3.56
3-4	518	1.27	0.41	0.72	2.22
5-6	459	1.25	0.44	0.71	2.19
7-8	366	0.87	0.73	0.41	1.88
9-10	353	0.66	0.26	0.32	1.36
11-12	295	0.75	0.49	0.34	1.67
13-14	213	0.71	0.45	0.29	1.74
15-16	206	0.76	0.53	0.32	1.80
17-18	165	0.36	0.11	0.10	1.28
19-20	92	4.00	0.03	1.18	13.56
21-22	69	0.31	0.28	0.04	2.65
23-24	25	1.56	0.68	0.20	12.33

Appendix 6.2

Table: Association of penicillin resistance with 3 groups of beta lactam use: only penicllin use, only cephalosporin use and both penicillin and cephalosporin use during the 2 months prior to swab collection, adjusting for cluster effect of the children

Types of beta-lactam use	Total isolate	OR	P	Lower 95% CI	Upper 95% CI
Only penicillin	461	1.63	0.29	0.66	4.01
Only cephalosporin	475	1.93	0.08	0.93	3.98
Both penicillin and cephalosporin	434	4.67	0.02	1.27	17.09

Appendix 6.3

Table: Effect of penicillin group use alone during each two monthly period on penicillin resistance, adjusting for the cluster effect of repeated positive isolate from a child

Time before swab collection (months)	Total isolate	OR	P value	Lower 95% CI	Upper 95% CI
0-2	461	1.63	0.29	0.66	4.01
3-4	447	1.63	0.23	0.73	3.67
5-6	398	1.53	0.26	0.73	3.23
7-8	330	0.67	0.47	0.22	1.99
9-10	304	0.58	0.28	0.21	1.57
11-12	263	0.87	0.77	0.34	2.22
13-14	177	0.46	0.32	0.10	2.12
15-16	168	0.45	0.31	0.10	2.07
17-18	122				
19-20	84	2.1	0.40	0.37	11.81
21-22	64	0.5	0.54	0.06	4.51
23-24	22	1.17	0.91	0.09	15.41

*None of the isolates that had penicillin use was resistant to penicillin.

Appendix 6.4

Table: Effect of cephalosporin use alone during each two monthly period on penicillin resistance, adjusting for the cluster effect of a child

Time period before swab collection (months)	Total isolate	OR	P value	Lower 95% CI	Upper 95% CI
0-2	475	1.93	0.08	0.93	3.98
3-4	465	0.90	0.80	0.39	2.06
5-6	402	0.91	0.83	0.39	2.15
7-8	322	1.44	0.49	0.52	4.01
9-10	289	0.31	0.13	0.07	1.38
11-12	241	0.25	0.19	0.03	1.94
13-14	180	0.64	0.50	0.18	2.32
15-16	172	1.09	0.88	0.38	3.14
17-18	141	0.30	0.25	0.04	2.36
19-20	82	9.78	0.007	1.86	51.48

Appendix 6.5

Table: Effect of combined penicillin group and cephalosporin use during each 2 monthly period on penicillin resistance, adjusting for the cluster effect of repeated pneumococcal isolates from the same child

Time period before swab collection (months)	Total isolate	OR	P value	Lower 95% CI	Upper 95% CI
0-2	434	4.67	0.02	1.27	17.09
3-4	420	1.96	0.32	0.52	7.41
5-6	357	1.99	0.40	0.40	9.98
7-8*	255				
9-10	266	2.37	0.17	0.69	8.14
11-12	225	1.93	0.44	0.37	10.16
13-14	158	2.23	0.36	0.40	12.29
15-16	152	0.65	0.69	0.08	5.49
17-18	129	4.43	0.15	0.59	33.36
19-20*	67				
21-22	64	0.5	0.54	0.06	4.51
23-24	22	1.17	0.91	0.09	15.41

*no penicillin resistant isolates in the exposed group

Appendix 6.6

Table: Penicillin resistance in pneumococci isolated from four groups of children, grouped by the duration of beta lactam use during the six months before swab collection (n=456 isolates)

Penicillin sensitivity	0 days (%)	1-7 days (%)	8-14 days (%)	>14 days (%)
Total isolates	257	64	74	61
Sensitive	225 (88)	57 (89)	61 (82)	45 (74)
Resistant	32 (12)	7 (11)	13 (18)	16 (26)

Appendix 6.7

Table: Rate of penicillin resistance among four groupos of isolates, grouped by the duration of total penicillin use during the six months before swab collection (n=333 isolates)

Penicillin sensitivity	0 days (%)	1-7 days (%)	8-14 days (%)	>14 days (%)
Total isolates	257	32	28	16
Sensitive	225 (88)	28 (87)	23 (82)	11 (69)
Resistant	32 (12)	4 (13)	5 (18)	5 (31)

Appendix 6.8

Table: Effect of total penicillin group use alone during the six months prior to the swab collection on penicillin resistance, adjusting for cluster effect of repeated pneumococcal isolates from the same child (n=333 pneumococcal isolates)

	OR	Robust std err	P value	Lower CI	Upper CI
Penicillin use alone in 6 months	1.04	0.02	0.03	1.00	1.09

Appendix 6.9

Table: Rate of penicillin resistance among four groupes of isolates, grouped by the duration of total cephalosporin use during the six months before swab collection (n=343 isolates)

Penicillin sensitivity	0 days (%)	1-7 days (%)	8-14 days (%)	>14 days (%)
Total isolates	257	30	40	16
Sensitive	225 (88)	27 (90)	33 (83)	13 (81)
Resistant	32 (12)	3 (10)	7 (17)	3 (19)

Papers

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Antibiotic resistance in *Streptococcus pneumoniae* isolated from children

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Objective: To determine the level of antibiotic resistance in *pneumoniae* (*S. pneumoniae*) isolated from nasal swabs of healthy children.
Method: Cross-sectional community survey.
Setting: Survey was undertaken in general practice settings in Canberra during March and April 1998.
Subjects: Four hundred and sixty-one children under 3 years of age enrolled in a general practice trial of clinical practice guidelines for antibiotic use.
Outcome measures: Resistance to penicillin, erythromycin, co-trimoxazole, tetracycline, chloramphenicol and cefotaxime among the isolates of *S. pneumoniae*.
Results: A total of 461 nasal swabs were collected and *S. pneumoniae* was isolated from 171 (37.1%). Penicillin resistance was found in 12.3% of these isolates, with high level resistance in 0.6%. Resistance rates were higher for cotrimoxazole (44.4%) and erythromycin (18.1%) than for penicillin. Multidrug resistance was found in 19% of these isolates. There was a significant association between the attendance at a day care centre and carriage of pneumococcus (53% vs 32%, odds ratio (OR) 2.4, 95% confidence interval (CI)1.5–3.7, $P < 0.001$). Children who attended day care centres and had received antibiotics during the 4 months prior to swab collection were three times more likely to carry an antibiotic-resistant isolate than children who had neither attended a day care centre nor received antibiotics (68% vs 40%, OR 3.1, 95% CI 1.2–8.4, $P = 0.02$).
Conclusion: The level of antibiotic resistance in pneumococci from healthy children was of concern. Carriage of pneumococcus was significantly higher in children who attended a day care centre. Resistance was significantly correlated with antibiotic use in combination with day-care attendance. These findings warrant more judicious use of antibiotics in children.

Key words: antibiotic; children; pneumococci; resistance.

Streptococcus pneumoniae (*S. pneumoniae*) is a leading cause of morbidity and mortality worldwide, especially in children.[1] *S. pneumoniae* is the single most-common cause of otitis media, pneumonia, meningitis and bacteraemia in young children.[2] Although a strain of *S. pneumoniae* resistant to penicillin was first reported in 1967 in Australia,[3] resistant strains have become more prevalent since 1987.[4] Prescription of antibiotics is directly related to the rate of development of resistance[5,6] and frequent or long-term use of antibiotics is a significant risk factor for the development of resistance.[7–9] Young children are more likely to be colonized with antibiotic-resistant organisms[1,10] and attendance at day care centres has been identified as a factor in the spread of resistant organisms between children.[2,8,11,12]

Respiratory infection is the most common diagnosis in Australian children,[13] particularly during winter. Antibiotics are widely prescribed to treat common respiratory infections, most of which are of viral in origin.[4,14,15] As in other developed countries, antibiotic use in Australia is high;[16] for example, 77% of cases of acute otitis media are treated with antibiotics.[13] The incidence o acute otitis media is associated with increased nasopharyngea colonization of pneumococci and penicillin resistance is signifi cantly related to an increased incidence of unresolved otiti media.[1]

While antibiotic resistance has become a major public healt problem, relatively little work has been reported in outpatien settings to ascertain the level of antibiotic resistance to pneumo cocci among Australian children.[17] This study was conducted ir general practice settings to determine the rate of pneumococca colonization, the pattern of antibiotic resistance in pneumococc and the relationship of resistance to antibiotic use in children.

METHODS

This study was undertaken in the course of a randomized controlled trial in Canberra, which is investigating the effects o clinical practice guidelines on antibiotic prescribing in acut respiratory infections in general practice. The trial commenced ir September 1997. A total of 54 randomly selected general practi tioners (GP) from Canberra subsequently recruited 500 children under 2 years of age from their practices. Informed consent wa obtained from the parents during recruitment. At study entry parents completed a questionnaire which included general infor mation about their children. The respiratory health of the childre

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was followed for a period of 2 years using a series of daily diaries, which are being maintained and returned by their parents every month. Parents recorded various symptoms of respiratory infections that their children suffered during the study period. They also reported antibiotic use and duration of treatment. Before implementing the intervention, nasal swabs were collected during March and April 1998, from healthy children, to detect the baseline level of resistance in pneumococcus. These swabs formed the basis for this study. Nasal swab collection was approved by the Ethics in Human Experimentation Committee.

Nasal swabs were collected by moistening the swab in Amies transport media (Interpath Services Pty Ltd, Melbourne, Australia) and then placing the swab directly on the blood agar plate containing 5 μg/mL of gentamicin. The child's name, age, sex, and date of birth were recorded. Specimens were immediately inoculated in blood agar plates and incubated for 18 to 24 h at 35°C in an atmosphere with added 5% CO_2. *S. pneumoniae* was identified by colonial morphology, α-haemolysis on blood agar plates, susceptibility to optochin and/or bile solubility. The predominant colony-type of each isolate was tested for susceptibility to penicillin, erythromycin, co-trimoxazole, tetracycline, chloramphenicol and cefotaxime. Susceptibility testing was performed on Mueller–Hinton Agar with 5% defibrinated sheep blood (MHASB), according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[18] Penicillin and erythromycin susceptibility were also tested using E-strips for each isolate. The breakpoints for minimal inhibitory concentration (MIC) published by NCCLS guidelines were used.[19] The isolates were defined as sensitive to penicillin when MIC was less than or equal to 0.064 mg/L, intermediate when MIC was greater than 0.064 mg/L but less than or equal to 1 mg/L, and highly resistant when MIC was greater than 1 mg/L. All isolates were tested for cefotaxime susceptibility with a 30 μg disc and those that were penicillin resistant were also tested with a cefotaxime E-strip. Antibiotic resistance was categorized as either intermediate or high level resistance. Multidrug resistance was defined as the presence of intermediate or high level resistance to two or more antibiotics.

Parent questionnaires and diary data were analysed over 4 months between January to April to ascertain antibiotic use and attendance at day care for comparison with swab culture and sensitivity results. We considered that antibiotic use during the preceding 4 months could affect antibiotic resistance, based on the fact that the half-life of naso-pharyngeal carriage of a pneumococcal strain is 2–5 months.[20] Pearson Chi-square tests were used to compare percentages between groups. Mann–Whitney tests were used to compare the distribution of antibiotic use between groups. Odds ratios (OR) were calculated to measure the association between various risk factors and resistance. All calculations were performed using SPSS 7.5 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Nasal swabs were collected from 461 children, representing 92% of the children participating in the trial. The mean age of the children was 11.7 months ranging from 0.5 months to 27.4 months. Of the 461 children 43.6% were male. *Streptococcus pneumoniae* was isolated from 171 of the swabs collected (37.1%). The overall rate of penicillin resistance was 12.3%, with high level resistance in 0.6% of isolates (Table 1).

Isolates also showed resistance to antibiotics other than penicillin. Forty-nine per cent of the isolates were resistant to one or more of the antibiotics tested. Among these isolates, 19% were multiresistant and 1% of isolates were resistant to all antibiotics tested (Table 2).

Most of the penicillin-resistant isolates ($n = 21$) were also resistant to other antibiotics, 91% (19/21) were resistant to co-trimoxazole, 67% (14/21) were resistant to erythromycin, 14% (3/21) to chloramphenicol, 62% (13/21) to tetracycline and 10% (2/21) to cefotaxime either alone or in combination. The resistance patterns are shown in Table 3.

A total of 38% (57/150) of the penicillin-sensitive isolates were resistant to co-trimoxazole, 11% (17/150) to erythromycin, 4% (6/150) to tetracycline, either alone or in combination (Table 3). All penicillin sensitive isolates were also sensitive to chloramphenicol.

There were no significant differences in age, sex or and breast-feeding status between children with sensitive and those with resistant isolates. We found a significant relationship between day care centre attendance and isolation of pneumococcus. Pneumococcus was isolated from 53% (60 of 113) of the children who attended a day care centre, and from 32% (103 of 318) of those who did not (OR 2.4, 95% CI 1.5–3.7, $P < 0.001$). There was no significant difference in pneumococcal carriage rate between children who attended family day care and those who had home care, although the number of children who attended family day care was very small (only six children).

Antibiotic resistance was more common in isolates from children who attended day care; 58% (35/60) were resistant to one or more antibiotics, compared to 44% (45/103) of those isolates children were cared for at home. The trend was not statistically significant (OR 1.8, CI 0.95–3.4, $P = 0.07$). Three out of six isolates from children who attended family day care were resistant to at least one antibiotic (OR 1.3, CI 0.25–6.7, $P = 0.8$). The level of antibiotic resistance did not show a significant relationship with duration of day care attendance.

Information regarding antibiotic use during the 4 months prior to swabbing was available for 157 of 171 children from whom *S. pneumoniae* was isolated. Of these, 78 children carried resistant and 79 carried sensitive isolates. Forty-one per cent of children with resistant isolates had received at least one day of antibiotic treatment compared with 29% of children with sensitive isolates (Fig. 1). Nine percent of the children with resistant isolates received antibiotics for at least 20 days compared to only 3% of the children with sensitive isolates (Fig. 1). The children carrying resistant pneumococci tended to receive more days of treatment with antibiotics than those with sensitive isolates (mean 8.5 days *vs* 3.8 days, $P = 0.07$). Two children had been taking antibiotic prophylaxis (> 90 days) and both were in the group that carried resistant isolates. When these two children were excluded, children with resistant isolates still had more days of antibiotic use than those with sensitive isolates (mean 5.6 days *vs* 3.8 days, $P = 0.1$) and 57% of children who received antibiotics for at least one day carried resistant strains compared with 45% of those who had received no antibiotics ($P = 0.2$).

Children who attended day care centres and received antibiotics during the 4-month period were three times more likely to carry a resistant isolate than the children who neither attended a day care centre nor received antibiotics (68% *vs* 40%, 17/25 *vs* 25/62, OR 3.1, CI 1.2–8.4, $P = 0.02$).

Table 1 Sensitivity of pneumococcal isolates to antibiotics in children

Sensitivity result	Penicillin (%)	Erythromycin (%)	Co-trimoxazole (%)	Tetracycline (%)	Chloramphenicol (%)	Cefotaxime (%)
Sensitive	150 (87.7)	140 (81.9)	95 (55.6)	152 (88.9)	168 (98.2)	169 (98.8)
Intermediate resistant	20 (11.7)		10 (5.8)	2 (1.2)		1 (0.6)
Highly resistant	1 (0.6)	31 (18.1)	66 (38.6)	17 (9.9)	3 (1.8)	1 (0.6)

Minimal inhibitory concentration breakpoints:
Penicillin: Sensitive ≤ 0.064 mg/L; intermediate ≥ 0.064–1 mg/L; highly resistant > 1 mg/L.
Erythromycin: Sensitive ≤ 0.250 mg/L; intermediate ≥ 0.250–1 mg/L; highly resistant > 1 mg/L.
Cefotaxime: Sensitive ≤ 0.50 mg/L; intermediate ≥ 0.50–1 mg/L; highly resistant > 1 mg/L.

Table 2 Pneumococcal isolates resistant to the number of antibiotics

Number of antibiotics to which the isolate showed resistance	Number and percentage of resistant isolates (%)
0	87 (51)
1	52 (30)
2	13 (8)
3	6 (4)
4	11 (6)
6	2 (1)

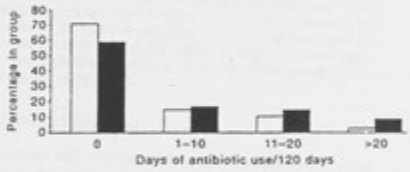

Fig. 1 Percentage distribution of antibiotic use for children according to their resistance status. (□), non-resistant (n = 79; (■), resistant (n = 78).

DISCUSSION

The only other Australian study that has looked at pneumococca resistance to commonly prescribed antibiotics in children took place in 1993.[17] The unique feature of the present study is that i has also looked at the antibiotic usage of the children before the swab tests, which highlights the effect of antibiotic use on antibiotic resistance.

The rate of antibiotic resistance in *S. pneumoniae* has been increasing in Australia, although at a slightly slower rate than in some areas of the USA.[21,22] The level of penicillin resistance in isolates from children in this study was substantially higher than the level found in a study of preschool children in Australia in 1993, in which 5% of the isolates of *S. pneumoniae* were resistant to penicillin.[17]

Resistance to erythromycin, co-trimoxazole, tetracycline and chloramphenicol has also increased over the last 5 years.[1] Pneumococcal resistance to erythromycin, chloramphenicol and tetracycline is chromosomally mediated and can be transferred by conjugal transposition.[23] This could explain our finding of tetracycline and chloramphenicol resistance in our study children, although these drugs are not usually prescribed to the children in this age group. Moreover, resistance to these drugs can be due to the selective pressure of the aminopenicillins; due to sharing of resistance mechanisms for several drugs in the same organism.[6]

We have not tested isolates for susceptibility to first and second generation cephalosporins, as the results can be extrapolated from penicillin resistance. We found little cefotaxime

Table 3 Resistance to other antibiotics among penicillin-sensitive and penicillin-resistant isolates

Antibiotics other than penicillin to which resistant	Penicillin-sensitive isolates (%) (n = 150)	Penicillin-resistant isolates (%) (n = 21)
None	58 (87)	9.5 (2)
Co-trimoxazole	30 (45)	19 (4)
Erythromycin	3.3 (5)	
Erythromycin + co-trimoxazole	4.7 (7)	9.5 (2)
Erythromycin + tetracycline	0.7 (1)	
Erythromycin + co-trimoxazole + tetracycline	2.7 (4)	47.6 (10)
Chloramphenicol + co-trimoxazole + tetracycline		4.8 (1)
Co-trimoxazole + tetracycline	0.7 (1)	
Erythromycin + co-trimoxazole + tetracycline + chloramphenicol + cefotaxime		9.5 (2)

resistance in our study (1.2%), and this is slightly higher than the rate found in a larger study by Collignon during 1994–95, in which 0.7% of pneumococcal isolates were resistant to cefotaxime.[21] In that study there was no high level resistance to cefotaxime, whereas one of the two isolates in our study showed high level cefotaxime resistance. We tested cefotaxime resistance only in isolates that showed either intermediate or high level resistance to penicillin, as the mechanism of resistance is usually similar for penicillin and third generation cephalosporin, that is, changes in penicillin-binding proteins.[23]

Our study showed a trend that the children with resistant isolates had more days of antibiotic use than the children with sensitive isolates. This is not surprising and supported the widely held view that consumption of antibiotics is an important factor for development of resistance.[5] Our finding also reinforced the evidence that long-term use of antibiotics is a significant risk factor for development of resistance.[26]

This study showed a trend towards a higher prevalence of antibiotic-resistant pneumococci in children attending day care centre, which was of borderline significance ($P = 0.07$). This association of antibiotic resistance with day care centre attendance has been supported in other studies.[10,11] A greater proportion of children who attended day care centre carried isolates that were resistant to one or more antibiotics compared to the children who had home care. Though neither antibiotic use nor attendance at day care centre independently had a significant relationship to resistance, the combination of both factors showed a highly significant association with antibiotic resistance. This has important implications in treating children in countries like Australia, where a high proportion of children attend day care centres.

Antibiotic use should be judicious. We need to educate both patients and GP to reduce unnecessary antibiotic use, before antibiotic resistance rises to even more alarming levels in this community. The study of which the present study was a part has been designed to explore the impact of clinical practice guidelines on antibiotic-prescribing, which is implemented to one group of GP and parents.

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REFERENCES

1 Zenni MK, Cheatham SH, Thompson JM *et al.* Streptococcus pneumoniae colonization in the young child: Association with otitis media and resistance to penicillin. *J. Pediatr.* 1995; 127: 533–7.

2 Radetsky MS, Istre GR, Johansen TL *et al.* Multiply resistant pneumococcus causing meningitis: its epidemiology within a day-care centre. *Lancet* 1981; 10: 771–3.

3 Hansman D, Bullen MM. A resistant pneumococcus. *Lancet* 1967; 2: 264–5.

4 McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office based physicians in the United States. *JAMA* 1995; 273: 214–9.

5 Seppala H, Klaukka T, Vuopio-Varkila J *et al.* The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N. Engl. J. Med.* 1997; 337: 441–6.

6 Baquero F, Martinez-Beltran J, Loza E. A review of antibiotic resistance patterns of Streptococcus pneumoniae in Europe. *J. Antimicrob. Chemother.* 1991; 28 (Suppl. C): 31–8.

7 Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996; 313: 387–91.

8 Tan TQ, Mason EO, Kaplan SL. Penicillin resistant systematic Pneumococcal infections in children: A retrospective case-control study. *Pediatrics* 1993; 92: 761–7.

9 Reichler MR, Allphin Aa, Breiman RF *et al.* The spread of multiply resistant Streptococcus pneumoniae at a day care center in Ohio. *J. Infect. Dis.* 1992; 166: 1346–53.

10 Mainous AG, Evans ME, Hueston WJ, Tilow WB, McCown LJ. Patterns of antibiotic-resistant Streptococcus pneumoniae in children in a day-care setting. *J. Fam. Prac.* 1998; 46: 142–146.

11 Henderson FW, Gilligan PH, Wait K, Goff DA. Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care. *J. Infect. Dis.* 1988; 157: 256–63.

12 Barnes DM, Whittier S, Gilligan PH, Soares S, Tomasz A, Henderson FW. Transmission of multidrug-resistant serotype 23F Streptococcus pneumoniae in group day care: Evidence suggesting capsular transformation of the resistant strain in vivo. *J. Infect. Dis.* 1995; 171: 890–6.

13 Bridges-Webb C, Britt H, Miles DA, Neary S, Charles J, Traynor V. Morbidity and treatment in General Practice in Australia 1990–91. *Med. J. Aust.* 1992; 157 (Suppl.): 1–57.

14 Nyquist A-C, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA* 1998; 279: 875–7.

15 McGregor A, Dovey S, Tilyard M. Antibiotic use in upper respiratory tract infections in New Zealand. *Family Prac.* 1995; 12: 166–70.

16 McManus P, Hammond ML, Whicker SD, Primrose JG, Mant, A, Fairall SR. Antibiotic use in the Australian Community, 1990–95. *Med. J. Aust.* 1997; 167: 124–7.

17 Hammond ML, Norriss MS. Antibiotic resistance among respiratory pathogens in preschool children. *Med. J. Aust.* 1995; 163: 239–42.

18 National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests. Approved standard. Document M2–A5. 5th edn. National Committee for Clinical Laboratory Standards, Villanova, PA, 1993.

19 National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing. 5th informational supplement. Document M100–S5. National Committee for Clinical Laboratory Standards. Villanova, PA, 1994.

20 Brook I, Gober AE. Prophylaxis of Amoxicillin or Sulfisoxazole for otitis media: Effect on the recovery of Penicillin resistant bacteria from children. *Clin. Infect. Dis.* 1996; 22: 143–5.

21 Collignon PJ, Lell JM. Drug resistant Streptococcus pneumoniae: the beginning of the end for many antibiotics? *Med. J. Aust.* 1996; 164: 64–7.

22 Hofmann J, Cetron MS, Farley MM *et al.* The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N. Engl. J. Med.* 1995; 333: 481–6.

23 Klugman KP. Pneumococcal resistance to antibiotics. *Clin. Microbiol. Rev.* 1990; 3: 171–9.

RESEARCH

Realities of practice

Engaging parents and GPs in developing clinical practice guidelines

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OBJECTIVE To integrate evidence based medicine with the experience and expectations of consumers and GPs in the development of clinical practice guidelines for acute respiratory infections (ARI) in young children.
METHOD Focus groups and workshops were held with 21 GPs and 27 parents of young children involved in a 2 year randomised controlled trial.
RESULTS The acceptability of the guideline development process for participants was determined. Barriers were identified which would impede clinical change, including: inadequate time; lack of knowledge; fear of patient dissatisfaction; and fear of poor health outcome.
CONCLUSION This paper details a process of guideline development that addresses the realities of general practice in Australia and the concerns of consumers. We identified potential barriers to change and integrated intervention strategies with the evidence to produce realistic clinical practice guidelines.

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The development of clinical practice guidelines (CPGs) has gained momentum over the past decade in Australia and other countries but their effectiveness for improving clinical practice varies considerably.[1] Although Australian GPs generally have a positive attitude toward CPGs, they consider their impact for changing everyday clinical practice as low.[2] Low levels of compliance with CPGs have been attributed to many factors. Some clinicians feel guidelines diminish clinical autonomy, are irrelevant to everyday practice, have been developed by experts who do not understand the needs of GPs, or could be used against them in litigation.[3,4]

CPGs have often been developed with little planning for distribution and implementation, although in recent years, researchers have begun to address these shortcomings.[1] A sense of ownership, scientific validity, and a multifaceted approach to development and implementation are now acknowledged as important factors if CPGs are to change clinical practice.[4,5] Social, psychological and managerial theories have informed methods for changing clinical practice.[6–10] A multifaceted approach for the successful implementation of CPGs requires assessment of the barriers to change in the target population[11,12] and development of appropriate implementation strategies that address these barriers to change.[10,13,14]

This paper reports on a process of guideline development and implementation using an evidence based method that addresses the realities of general practice in Australia and the concerns of consumers.

Methods

The sample

This research was conducted as part of a 2 year randomised controlled trial (RCT) in Canberra, ACT, investigating the development and implementation of CPGs and their effect on the care and management of acute respiratory infections (ARI) in young children. GPs were randomly chosen from a database compiled from:

- a membership list from the ACT division of general practice,
- a list of practices from the ACT immunisation registry,
- and the *Yellow Pages* listings.

Each GP then recruited up to 15 of their patients under 2 years of age. In total 54 GPs and 500 children were involved in the RCT. The GPs along with their patients were randomly allocated to the intervention arm of the study (the group helping to develop clinical practice guidelines) or to a control group. The group of GPs and parents described here were in the intervention arm of the study.

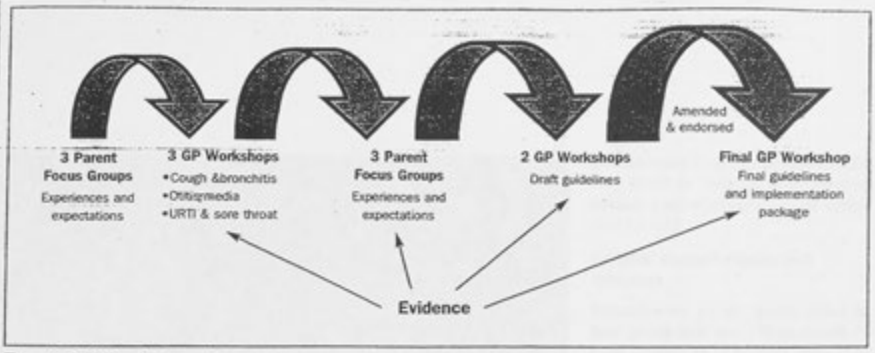


Figure 1. Guideline development process.

At recruitment, both GPs and parents completed study entry questionnaires which detailed characteristics of the GPs and their practices, and sociodemographic information of the study children and their families.

Study design

The process of guideline development involved a series of focus groups with parents, and workshops with GPs. A series of three focus groups for parents were held in various locations in Canberra. Parents were contacted by phone and invited to attend one of these. Next, three GP workshops were held as lunchtime meetings. A letter and follow up phone calls invited all the GPs from the intervention group to attend one of these workshops. Short summaries of the evidence for antibiotic treatment of ARI, derived where available from the Cochrane Library, were sent to the GPs before the meetings to facilitate discussions. A second set of three parent focus groups was held a fortnight after the first GP workshops. A month later two more GP workshops were held as evening sessions. Three weeks later the final guideline development meeting was held for the GPs to amend and endorse the guidelines. Thus GPs were invited to attend up to three of the six workshops and parents were invited to attend one of the six focus groups.

These meetings built cumulatively on one another and explored the experiences and expectations of parents and GPs when caring for young children with ARI, and the evidence about the treatment of ARI. *Figure 1* illustrates the format of these meetings.

Initial meetings

The first set of three parent focus groups explored parents' experiences in caring for their young children with ARI, their concerns about the illness, home nursing used, and their expectations of care from their GP. This information plus evidence on the treatment of ARI, derived largely from Cochrane Systematic Reviews,[15-17] was used in the first three GP workshops. Each workshop concentrated on a different aspect of ARI:

- cough and acute bronchitis
- acute otitis media
- sinusitis
- sore throat.

The next step

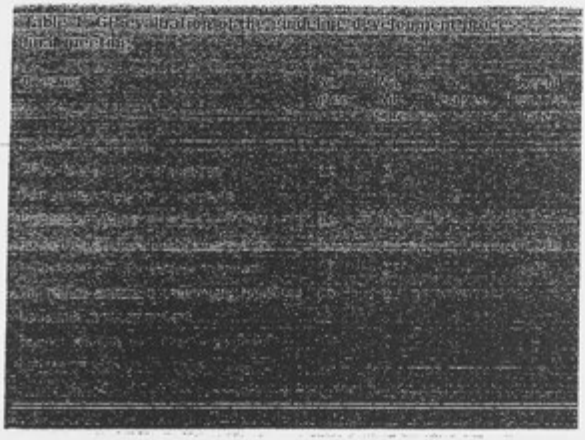
A second set of three parent focus groups further explored parents' experiences and expectations for ARI and their views on the evidence that had been discussed at the GP workshops. Two more GP workshops followed, where the evidence was explored further and draft guidelines were developed. At one of these workshops, a professor of general practice who is a Cochrane reviewer presented the evidence on otitis media and sore throat.

The final phase

The workshops and focus groups culminated in a final meeting for GPs. In this, they:

- edited a 'Principles of Practice' document for GPs
- approved guidelines for parents
- approved an implementation package containing educational materials, posters and clinical consultation aids.

An infectious disease specialist and a professor of paediatrics attended this final meeting to answer questions and facilitate discussion. The specific objective of the GP meetings was to develop the guidelines for GPs and parents, using evidence of best practice for



ARI and incorporating consumer and GP experiences and expectations. The objective of the parent focus groups was to understand parents' concerns for their children and their usual management practices when their children were ill with an ARI.

All meetings were audio-recorded and transcribed. The transcripts were coded and grouped to identify themes. Three of the authors (EJW, DN, CB) discussed and verified the themes and barriers identified.

Evaluating the process

Evaluation questionnaires on the guideline development process were distributed to the GPs attending the final meeting. Parents participating in the focus groups were also sent an evaluation questionnaire 1 month after receiving the parent guidelines. Evaluation questionnaires were based on previously tested questionnaires from continuing medical education events. Results from these evaluations and the parent and GP study entry questionnaires were analysed with the assistance of SPSS software.

Results

The GPs

Twenty-one of the 24 GPs who had been randomly allocated to the intervention group participated in developing guidelines. Of the 21 GPs attending any meeting, 17 (81%) attended two or three of the three guideline development sessions. Of the 21 GPs, 47.6% were female. Over half of the participants worked in small group practices (2–3 GPs) and spent an average of 40.3 hours per week in the surgery. All were vocationally registered and 95% were members of the ACT division of general practice.

The GP response to the process was extremely favourable. *Table 1* shows the results from the evaluation questionnaire from 17 of the 18 GPs who attended the final guideline meeting. At the end of the process, all were concerned about antibiotic resistance and 16 felt the process was informative, enjoyable, and relevant to their practice. Fifteen of the respondents said that consumer input was important in the development of guidelines and 16 of the respondents said they would be changing their practice towards a more judicious use of antibiotics for ARI.

Parents' characteristics and response

Twenty-seven parents participated in focus groups from over 150 contacted. A large percentage of parents were well educated (43.4% of mothers and 34.8% of fathers had university or postgraduate degrees) and earned an above average income. The study child was their first child for over half the parents attending the focus groups. The average age of the mothers was 32 years (range 19–39 years). Thus the parents who attended the focus groups were better educated and in a higher socioeconomic group than the average Australian, or the average Canberran.[8]

The parents' response to their involvement in the guideline development process was also favourable. More than 90% of the respondents felt the process was informative, enjoyed interacting with other parents, and were concerned about antibiotic resistance. Nearly 67% said they gained valuable new knowledge on ARI and now felt more confident in caring for their sick children. Although only 30% of the parents felt they could communicate better with their GP, several of these respondents commented that they already had very good communication with their doctor. In the evaluation questionnaire, some parents mentioned that more information at the outset would have been useful and felt the discussions were one-sided. At the parent focus group stage of the process, the researchers were careful not to give the parents clinical advice.

Identified barriers

Through a systematic analysis of the transcripts from all the focus groups and workshops, we identified several factors

that could impede the successful implementation of evidence based guidelines into clinical practice. *Table 2* lists the barriers identified, as well as some implementation strategies used to address these barriers.

Inadequate Time

GPs frequently cited time as a reason for prescribing antibiotics. Consultations for otitis media, for example, were often seen as a chance to 'catch up' on the backlog of patients in the waiting room. The doctor could examine the ear and write a prescription in a short period. The parents said they often expected antibiotics for this condition and therefore would accept a quick consultation. Other GPs felt that during the winter months they spent too much time explaining repeatedly to each patient about the viral aetiology and the ineffectiveness of antibiotic treatment for upper respiratory tract infections.

Lack of knowledge

With the flood of new information facing GPs, it can be difficult to stay abreast of all the latest evidence. The workshops provided an opportunity for comprehensive exploration of the evidence in relation to general practice.

Lack of knowledge was a big factor in parents' perceptions for the need for antibiotics. Although most parents seemed to understand that antibiotics were not effective for viral infections, there was some confusion about the aetiology of ARIs and signs and symptoms that may or may not indicate a bacterial infection.

Doubt about evidence

Some of the GPs felt the evidence in the literature, based on randomised controlled trials, presented an artificial situation. Others were sceptical about the criteria used for case inclusion in studies. They felt the conclusions from the research trials might not be relevant to everyday practice. There was much discussion about the validity of the studies, their definitions of disease and their applicability to everyday general practice:

> What I'm saying is a lot of the studies that say this is useless, (antibiotics for sore throat) take unrealistic definitions and have unprovable criteria for diagnosing disease or non-disease.

Fear of patient dissatisfaction

GPs expressed a fear that dissatisfied patients might defect to other doctors who may prescribe antibiotics more freely. GPs were also concerned about possible poor health outcomes if their approach towards ARI treatment became less interventionist:

> ...you'll lose that patient and you'll lose that family and you'll lose all their friends because it doesn't matter whether you made the right diagnosis or made a right decision, if that child ends up in hospital with pneumonia at any point... you're going to end up with angry parents at your doorstep.

Fear of litigation

Anxiety about litigation was an extension of the worry about losing patients and income and a concern for loss of prestige among their colleagues. Many GPs expressed the concern at the possibility of court action if they failed to prescribe an antibiotic. Other GPs felt specialists, who could testify against them in court, did not necessarily advocate the same treatment as was being developed for guidelines based on the evidence.

Reluctance to change

Underlying the other barriers was a general non specific fear of change, of practising medicine differently. Some GPs saw prescribing antibiotics for ARI as a safety net, an assurance they were treating a condition rather than being perceived by their patients as doing nothing. Others saw no need to change as they felt their practice was already evidence based.

Parental expectations of antibiotics

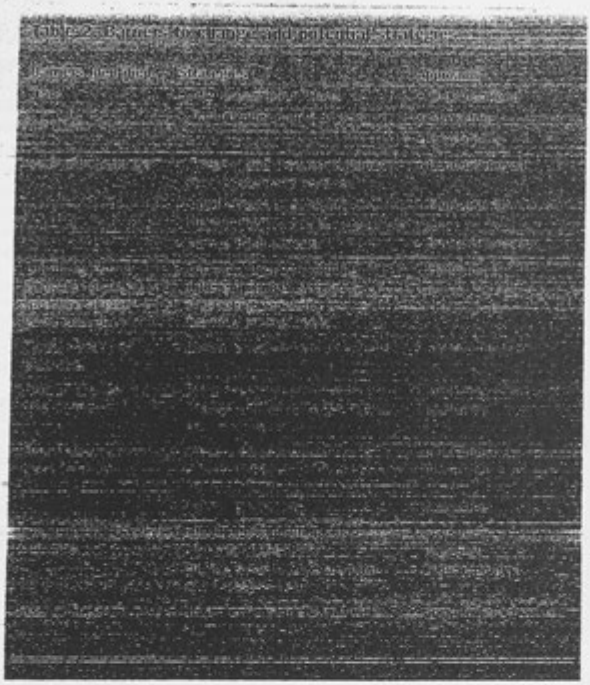
Parents often had definite ideas about when antibiotics were needed. In the case of a cough illness, most parents used nebulisers and chest rubs for several days at home before going to the doctor. If these home treatments did not work or the cough was accompanied by mucus then parents thought the infection required antibiotics:

> I always wait (to go to the doctor) until he gets green mucus.
>
> If it's a phlegm type cough I tend to think it's bacterial and doesn't really need the nebuliser but may need an antibiotic.

For many parents in the focus groups, earache was a major and repeated problem. They wanted a prescription for antibiotics and believed that antibiotics would clear up the problem quickly. This expectation of antibiotics for otitis media was often governed by the concern for serious complications from earache. Parents took what they believed to be preventive measures for earaches, including: wearing hats in winter; sterilising teats and bottles long after the recommended time; and avoiding getting water in their children's ears. In general, with the exceptions of otitis media and the presence of green mucus, parents were cautious about antibiotic treatment for ARI and desired a judicious use of antibiotics for their children.

Discussion

Several aspects of this development process are unique. Whereas GP focus groups or working groups have been used in guideline development before,[6,28] to our knowledge, consumer input has not been incorporated to this extent. Questionnaires showed GPs recognised the need for consumers to be active participants in the guideline process. Involving consumers in the development process gave GPs a better understanding of the



needs and expectations of their patients. Because they were informed by consumer expectations, the guidelines could address specific parental concerns and answer some common misconceptions.

The cumulative nature of the alternating parent and GP meetings allowed for reassessment and refinement of the issues discussed by the participants and thus produced guidelines that were relevant to GPs and consumers.

Another important aspect of this development process was inviting several experts to attend some of the GP meetings. These included an infectious disease specialist, a paediatrician, and a GP reviewer for the Cochrane Collaboration. Even though the GPs accepted responsibility for the guidelines, we feel the presence of these experts gave the GPs more confidence that leaders in the field would support them and the guidelines.

This approach to guideline development and implementation systematically investigated the barriers to change for the target group of GPs and consumers. We were able to use the identified barriers to devise specific implementation strategies to address these barriers. For example, we approached the problem of inadequate time by providing practitioners with patient information sheets on otitis media and sore throat and prescription-like pa These pads allowed the GP to tick a seri of boxes that explained the diagnosis, re ommended symptomatic treatment, a described warning signs if parents did n see any improvement.

The workshop format for the develo ment of the guidelines gave the GPs sense of ownership of the guidelines. Th workshops discussed the available ev dence for the treatment of ARI an explored variations in practice. GPs wh felt their practice was already evidenc based or who lacked the knowledge of th evidence, could explore those issue among their peers in a professionally sup portive environment. The presence o academic experts in evidence based medi cine, general practice, infectious disease and paediatrics at some of the workshop helped explain the details of publishe studies and strengthened the validity o the evidence for these GPs.

Potential patient dissatisfaction wa reduced by preparing a consumer version of the guidelines and a poster advocating judicious use of antibiotics for display in the GP's surgery. These helped to educate the consumers and inform them of any change in their GP's practice.

We encouraged GPs to use antibiotics less often as first line treatment in the mild cases by using a step-wise approach which would enable GPs to gain confidence in the new style of practice and provide empirical evidence that it did not produce poor health outcomes. We were also able to reassure the GPs that the results of their changed practice would be evaluated as part of the randomised controlled trial and they would be given feedback throughout the study. GPs in this study indicated that they planned to modify their prescribing practices. As the trial proceeds, we will be able to ascertain whether their actual prescribing practices have changed compared to GPs in the control arm of the study, who did not receive the guidelines or discuss them

until the intervention group had worked with them for a year.

This study demonstrates a process of guideline development that goes beyond a statement of best clinical practice. For evidence based health care to be implemented through clinical practice guidelines, all the aspects of decision making and behaviour change need to be explored and consolidated in a systematic way with the clinical evidence.

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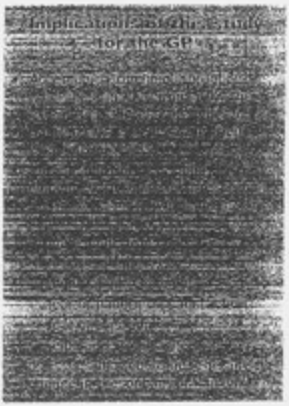
References

1. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342(8883):1317–22.
2. Gupta L, Ward JE, Hayward R. Clinical practice guidelines in general practice: a national survey of recall, attitudes and impact. Medical Journal of Australia 1997;166:69–72.
3. Tunis SR, Hayward RS, Wilson MC, Rubin HR, Bass EB, Johnston M, et al. Internists' attitudes about clinical practice guidelines. Ann Intern Med 1994;120(11):956–63.
4. Siriwardena AN. Clinical guidelines in primary care: a survey of general practitioners' attitudes and behaviour. Br J Gen Pract 1995;45(401):643–7.
5. Davis DA, Taylor Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Can Med Assoc J 1997;157(4):408–16.
6. Effective Health Care Bulletin. Implementing clinical practice guidelines: can guidelines be used to improve clinical practice? Leeds: Nuffield Institute for Health, University of Leeds; 1994 December 1994. Report No.: 8.
7. Grol R. Development of guidelines for general practice care. Br J Gen Pract 1993;43(369):146–51.
8. Robertson N, Baker R, Hearnshaw H. Changing the clinical behaviour of doctors: a psychological framework. Quality in Health Care 1996;5:51–54.
9. Firth-Cozens J. Healthy promotion: changing behaviour towards evidence-based health care. Qual Health Care 1997;6:205–211.
10. Conroy M, Shannon W. Clinical guidelines: their implementation in general practice. Br J Gen Pract 1995;45 (396):371–5.
11. Haynes R, Sackett D, Guyatt G, Cook D, Gray JM. Transferring evidence from research into practice: 4. Overcoming barriers to application. Evidence-Based Medicine 1997;2(3):68–69.
12. Armstrong D, Reyburn H, Jones R. A study of general practitioners' reasons for changing their prescribing behaviour. BMJ 1996;312:949–52.
13. Grol R. Personal paper. Beliefs and evidence in changing clinical practice. Bmj 1997;315(7105):418–21.
14. Wensing M, Grol R. Single and combined strategies for implementing changes in primary care: a literature review. Int J Qual Health Care 1994;6(2):115–32.
15. DelMar C, Glasziou P. Antibiotics for the symptoms and complications of sore throat: The Cochrane Library; 1996 January.
16. Glasziou P, Hayem M, Mar CD. Treatments for acute otitis media in children: antibiotic versus placebo: The Cochrane Library; 1996 1997. Report No.: 1.
17. Becker L, Glazier R, McIsaac W, Smucny J. Antibiotics for Acute Bronchitis. Acute Respiratory Infections Module of The Cochrane Database of Systematic Reviews 1997;4.
18. Jacobs D. Australian Capital Territory in Focus, 1998. Canberra: Australian Bureau of Statistics: 1998. Report No: 1307.8.
19. Fardy HJ, Jelfs D. Focus groups: a method for developing consensus guidelines in general practice. Fam Pract 1994;11(3):325–9.
20. Hungin AP, Rubin G, Russell A, Convery B. Guidelines for dyspepsia management in general practice using focus groups. British Journal of General Practice 1997;47:275–279.



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